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13. ABSTRACT (Maximum 200 Words)
Breast cancer remains a leading cause of death for women in the U.S. despite the popularity of mammography as a preventive tool. At diagnosis, many breast cancers are at an advanced stage of disease, even for women undergoing yearly screening, resulting in costly and painful follow-up procedures. Based on the ongoing studies in many research institutions, it has been shown that molecular markers can increase our ability to diagnose early stages tumors. This has been demonstrated by current clinical practices using the CA-125 marker and PSA for the detection of ovarian and prostate cancer, respectively. The purpose of this study is to search for breast cancer biomarkers and evaluate their effectiveness in detecting early stage carcinoma. By combining molecular diagnosis with current imaging analysis of breast tissue, we may further reduce the number of deaths as well as the number of women undergoing surgery and chemotherapy due to breast cancer. To date, we have created the infrastructure necessary for our interdisciplinary team of investigators to obtain study samples, characterize respective biomarkers, and efficiently communicate research findings. We have also increased the number of potential biomarkers and looked into more efficient and sensitive biotechnology that may better assist our study investigators.

14. SUBJECT TERMS
Early detection, serum markers, specimen repository, sensitivity, specificity, screening, circulating cells, antibody tests, molecular profiling, marker panel, mammography, biomarker evaluation

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Introduction

Although mammography significantly reduces its toll, breast cancer remains a leading cause of cancer mortality in the U.S. Many breast cancers are advanced at the time of diagnosis, even among women participating in screening. The discovery of molecular markers associated with breast cancer potentially increases our ability to diagnose early stage tumors. We are proposing that molecular diagnosis be combined with imaging to enhance our ability to identify breast cancer when it is most treatable, i.e. still localized to the breast. This study will test the hypothesis that use of a breast cancer biomarker panel can improve the performance of mammography in early detection of breast cancer. We will evaluate candidate markers that are most likely to reflect the malignant potential of the cell, including circulating tumor cells, growth factors associated with angiogenesis, and the presence of antibodies to oncogenic proteins known to be associated with aggressive disease such as Her2/neu and p53. Our aims are: 1) to validate and refine the ability of candidate biomarkers to predict disease status; 2) to evaluate panels of biomarkers for use as an adjunct to mammography, to detect all breast cancer at a highly curable stage; and 3) to identify the molecular signatures of benign, pre-invasive and invasive breast cancers and explore their associations with biomarkers in the panel.

Body

During the first year of this study, while awaiting human subjects approval to enroll women, investigators have focused on development of a robust infrastructure to support the scientific objectives of the study. Efforts have focused on the following areas: 1) monitoring the breast cancer biomarker literature for research developments on markers of interest, 2) refinement of study protocols and development of relationships with clinicians who will provide access to patients for the study, 3) development of an advocate program to facilitate communication among scientists, clinicians and consumers, 4) collaboration among investigators to develop epidemiological, pathology and clinical data collections instruments for the study, 5) development of a web-based database and adaptation of an existing specimen inventory and tracking system to accommodate breast specimens, and 6) development of a web-based knowledge management system to support communication between investigators.

Potential biomarkers are being evaluated by literature review. This study proposes to evaluate markers that have potential to contribute to a marker panel that is able to distinguish among women with healthy breasts and women with various breast conditions, including distinguishing benign from malignant disease. Several markers of interest were indicated at the time of proposal development, including mammaglobin, markers of vascularization, bioactive lysophospholipids, and antibodies to p53, Her2/neu and IGFBP-2. Although formal selection of markers for evaluation is not proposed to begin until the second year of the study, investigators are conducting regular literature reviews to identify potential additional markers of interest. Literature reviews have specifically focused on biomarkers that are highly expressed or under-expressed in serum and that characterize subgroups of ductal carcinoma in situ (DCIS) and invasive breast cancer. About 20 candidate markers have been identified, which are being evaluated for their suitability for evaluation. For example, Psoriasin (S100A7) is under consideration because it is associated with ER-negative invasive tumors and high-grade comedo-type DCIS, and because, it is secreted by cancer cells, has been detected in urine, and an antibody is available for it.

Study protocols have been refined through collaboration with the Office of Regulatory Compliance and Quality. Study investigators and staff have been in regular communication with the Office of Regulatory Compliance and Quality to obtain human subjects approval for the

Mammography Tumor Registry (MTR) and patient recruitment protocols. As of this report, the MTR protocol has received final approval, and the clinical/recruitment protocol is near final but not yet formally approved. This detailed and careful review process has led to several refinements in the study protocols, the most significant of which is clarification of the relationship of the MTR to the patient recruitment component, in light of the HIPAA regulations that became effective in April 2003. To meet HIPAA guidelines, the protocol was clarified to indicate that electronic data received through the MTR would only be used to obtain individual mammography data after a HIPAA authorization was received. Rather than using MTR data to determine initial eligibility for the study, we will use a short screening questionnaire completed by all potential study participants. Individual mammography data is used for a more sophisticated assignment of risk status, conducted after the participant has donated blood and consented to review of her mammography records.

Additional refinements and clarifications to the protocols that were discussed between study investigators and the Office of Regulatory Compliance and Quality include refinements to the study consent forms, clarification of the eligibility criteria and risk stratification guidelines, discussion of the origin and development process for data collection instruments, clarification of the role of Cedars Sinai Medical Center investigators, clarification of the guidelines for future use of specimens and data donated to the study, provision of information to support the classification of this study as minimal risk, documentation of the Certificate of Confidentiality for the MTR, and documentation of relevant state legislation covering the MTR. These refinements and discussions have taken place over the course of three formal written exchanges between study investigators and the Office of Regulatory Compliance and Quality, along with multiple telephone and e-mail communications. At this time of this report, the MTR protocol is final and has received human subjects approval. Final revisions were made to the patient recruitment protocol in late September, and at the time of this report we are awaiting notification of approval from Peter Marshall, Human Protections Specialist. Copies of the Mammography Tumor Registry and Clinical/Recruitment Protocols are included as Appendices A and B.

In addition to editing protocols for human subjects compliance, investigators have also begun to discuss operational details of the specimen collection protocol. A diagram outlining the logistics of specimen collection is attached as Appendix C.

Community physicians and clinical facilities are collaborating with the study. To establish the foundation for patient recruitment once final human subjects approval is received, investigators have begun working with radiologists and surgeons to develop patient recruitment plans that are feasible within specific clinical environments. Toward this end, Shirley Gough, Research Nurse, presented this study to oncologists and surgeons at the Swedish Medical Center Tumor Board. Dr. Urban presented the study to the Director of the Swedish Cancer Institute and to the Cancer Institute Steering Committee, and in both cases the study was well-received with clinicians confirming their willingness and enthusiasm to collaborate on the study. Collaborating surgeons have been updated on study progress by letter. In the next year, we will begin holding monthly Interdisciplinary Working Group meetings to facilitate regular scientific exchange between Center of Excellence investigators, other laboratory scientists, and community physicians.

Although human subjects approval is pending for the patient recruitment portion of this study, investigators have used another source of funding to collaborate with physicians at the Swedish Breast Care Center to develop a registry of potential study participants who are available for this and other research studies. All women who undergo mammograms at Swedish Breast Care Center are being invited to sign a Consent to be Contacted form which provides permission for researchers to maintain their name indefinitely in a confidential registry and invite them to

participate in future studies. Currently, there are 1,494 women in the registry. These women are potential candidates for this study. A report showing enrollment in the registry is included as Appendix D.

An advocate program is being developed. One of the goals of the Center of Excellence is to have a well-integrated advocate program focused on facilitating communication between scientists and consumers, increasing minority participation, and assisting investigators in ensuring the clinical relevance of the marker panel. To support this effort, Joan McAree was hired to coordinate advocate efforts for the study. Advocates are working closely with study staff to develop an appropriate recruitment protocol for study participants from culturally diverse communities. Advocacy outreach has been successful in building relationships within ethnic communities to understand their cultural beliefs as they pertain to participation in research. For example, Ms. McAree has met with Cierra Sisters, Inc., Cancer Information Service Partnership Program, International Community Health Services, and the King County Breast and Cervical Health Program Community Partners Group to discuss participation in research. By conveying a community perspective advocates foster a two-way communication, building a unique understanding between the research program and the consumer communities.

As a team effort, advocacy has assisted study staff in the development of study participant recruitment materials and outreach tools to communicate with the community in a meaningful and culturally sensitive way.

Efforts to develop a local core advocate group are underway. A relationship was established with the local affiliate of the Susan G. Komen Breast Cancer Foundation to pilot the breast cancer advocate program in conjunction with their annual survivor brunch. Materials have been developed inviting this target community of breast cancer survivors into the advocacy program. Advocates have established a set of objectives to define their collaboration with investigators and study staff. These objectives are to (1) Ensure that research studies have a positive impact on patients and the community, (2) Collaborate with researchers to translate research findings into appropriate clinical applications, (3) Increase participation in research among minority and underserved populations, (4) Assist in the development of study participant recruitment, educational and retention materials, and (5) Develop community outreach programs to facilitate communication between researchers and the community.

Epidemiologic, clinical and pathology data collection instruments have been developed. The baseline questionnaire for this study was adopted from a questionnaire already in use in an ovarian cancer screening trial. This was done in the interest of maintaining common data elements. Final review of this questionnaire by study investigators is currently underway and may result in refinements to the format of baseline questionnaire variables for higher quality data, although the basic information will remain the same. Clinical and pathology data collection instruments are also currently under development. Dr. Scott Karlan developed a pathology data collection form which has been reviewed for consistency with National Cancer Institute common data elements and is currently under review by study pathologists. A draft clinical data collection form is also currently under review by study epidemiologists and clinicians. The approved baseline questionnaire and drafts of other data collection instruments are included as Appendix E.

Programmers have developed a web-based interface to manage study data. During the first year efforts have focused on production of an infrastructure for web-based access to the study database whose modules include the epidemiologic, clinical, laboratory, and specimen data. The system uses a middle tier application serving as gatekeeper to the database has been developed, enforcing research and security rules. Development has focused on presenting data entry interfaces, such as

the baseline questionnaire, via thin client browser applications securely at remote access points. One fundamental decision has been not to collect patient identifiable information via remote access point, only from within the FHCRC firewall. Much energy has gone into developing data structures to accommodate data collection instruments designed and ready for use on this study. Effort has also gone into designing coordination of a Virtual Shared Specimen Repository with collaborating sites. Screen shots demonstrating the baseline data entry screens are included as Appendix F.

A web-based knowledge management system supports communication among investigators. Investigators in Seattle and Los Angeles have been in communication via monthly conference calls to discuss current literature, human subjects issues, data instrument development and scientific oversight for the study. Minutes for these conference calls are attached as Appendix G. The first annual all-investigator meeting is planned for January 30, 2004. The draft agenda for this meeting is attached as Appendix H. A private web-based FlexKB knowledge base has been established for collaborators on the study. A number of resources are being added to this site including reading topics, literature reviews, protocols, meeting minutes, presentations, important dates, and contact and background information on each collaborator.

A secure server has been set up to host the tracking system data and communication of aggregate reports between the FlexKB and the tracking system have been designed but not yet implemented as we are in the final testing/deployment phase of the first version of the new tracking system.

One critical design goal for this system is to provide each collaborating site with secure, private access to their entire data set (as entered into the tracking system) while at the same time providing aggregate reporting to the whole group. Discussions with IT staff and collaborators have led to a solution to this challenge that includes automated reports being written to secure directories only accessible by the relevant collaborators as well as a "common" secure directory where aggregate reports are written. Links to these reports will provided in the FlexKB and users will authenticate in order to retrieve them. A security plan is now in place and the final details are being discussed with the collaborating groups as certain aspects of the security measures depend on the computer equipment and software at each site.

Key Research Accomplishments

Year one of this study has focused on infrastructure development and start-up efforts. No research results are available at this time.

Reportable Outcomes

No manuscript, presentations or publications have yet resulted from this study. A web-based database to support informatics is currently under development.

Conclusions

No research conclusions are available at this time.

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Appendices

Appendix A Mammography Tumor Registry Protocol

Appendix B Clinical/ Recruitment Protocol

Appendix C Logistics of Specimen Collection

Appendix D Enrollment into the Registry

Appendix E Data Collection Instruments

Appendix F Baseline Data Entry (Screen Shots)

Appendix G Conference Call Meeting Minutes

Appendix H All-Investigator Meeting: Draft Agenda

Appendix A
Mammography Tumor Registry Protocol

Protocol

Center for the Evaluation of Biomarkers for

Early Detection of Breast Cancer

Funded by the Department of Defense
Study Number BC013002

Mammography Tumor Registry Human Subjects Procedures Protocol (IR# 3636)

1. **Protocol Title.** Mammography Tumor Registry Human Subjects Procedures Protocol

2. **Medical Product Phase.** Not Applicable

3. **Principal Investigator**

Nicole Urban, ScD
Fred Hutchinson Cancer Research Center

Names of Other Investigators

Martin McIntosh, PhD, Statistician
Fred Hutchinson Cancer Research Center

Garnet Anderson, PhD, Statistician
Fred Hutchinson Cancer Research Center

Mariann Drucker, MD, Radiologist
Swedish Breast Center

David Dwyer, MD, Radiologist (Contributed Effort)
Swedish Breast Center

Janice Stracener, MD, Radiologist, (Contributed Effort)
Swedish Breast Center

Names of Personnel with significant involvement in the research study

Steven B. Zeliadt, MPH, Informatics Manager
Fred Hutchinson Cancer Research Center

Carole Shaw Database Manager
Fred Hutchinson Cancer Research Center

Sue Peacock, MS, Statistical Research Associate
Fred Hutchinson Cancer Research Center

4. **Location of Study**

Fred Hutchinson Cancer Research Center
1100 Fairview Avenue North, MP-900
PO Box 19024
Seattle, WA 98109-1024

5. **Time Required to Complete**

The MTR is an ongoing database begun in 1994. The database will be ongoing through the duration of the project.

6. Objectives

The primary goal of the Center for the Evaluation of Biomarkers for Early Detection of Breast Cancer is to define a biomarker panel for use with mammography to detect all breast cancers at a highly curable stage.

The role of the Mammography Tumor Registry will be to continue to obtain electronic mammography record information on all women seen at volunteer radiology clinics and identify subsequent breast cancer outcomes for all women through linkage to the Surveillance, Epidemiology, and End Results (SEER) cancer registry for Western Washington, and the Washington State Cancer Registry. Ongoing feedback regarding mammography outcomes will be provided to participating radiologists.

Women who volunteer to participate in the Center of Excellence study at participating radiology facilities will be identified in the electronic data. Based on demographic, risk profile information, and mammography results in the data collected from the participating clinics, women will be sampled and contacted for biomarker specimen donation (see Protocol # 5317). These women will be flagged in the MTR database and subsequent mammography data and breast cancer outcomes will be monitored.

7. Study Population

The goal of this research is to provide valuable information to all women at risk for breast cancer and all health providers involved in their care regarding the performance of mammography and the contribution of a panel of biomarkers in the early detection of breast.

There are two main study populations involved in the MTR, 1) women obtaining mammograms and 2) radiologists interpreting the films. Among the women obtaining mammograms, a sub-group complete consent forms at the radiology clinic indicating they would be willing to participate in future research studies conducted at FHCRC such as the Center of Excellence study. This consent to contact process is described in Protocol #5317.

Currently in the MTR database there are 939,203 mammograms for 365,304 women. These records were provided by 14 radiology groups serving 75 radiology clinics across Washington State. These exams were read by 166 radiologists.

At the present time, we have established a process similar to informed consent for all radiologists requesting feedback reports regarding the follow-up breast cancer outcomes for his or her patients. As these research subjects are physicians and their participation is primarily a quality-assurance activity, this process was developed to clarify their responsibility in protecting the confidentiality of their patient's data, and explicitly prohibit use of the data for marketing purposes.

8. Protocol Design

a. Subject Identification

A data file will be produced containing a unique set of identifiers for women in mammography data files provided by volunteer facilities. The identifiers will be matched against CSS/WSCR breast cancer cases using a computer program designed to find potential matches on personal identifiers. All matches will be confirmed by a manual review performed under the supervision of the MTR Database Manager. For the

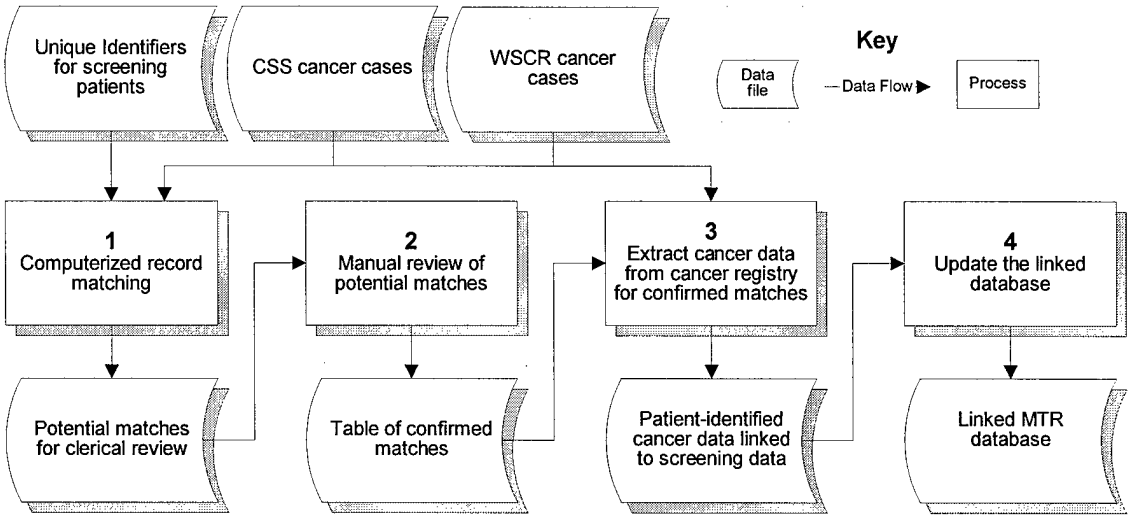
women conclusively linked to breast cancer cases, a data file will be generated from the CSS/WSCR database containing identifiers and selected cancer/pathology variables as well as additional follow-up care and administrative variables such as treatment date, site-specific surgery, vital status, date last followed, first course of treatment and reporting institution. The patient-identified data will undergo quality assurance checks and will be incorporated in the MTR linked database. The data linkage process is described in Figure 1.

The computerized record-matching portion of the linking process will be performed by the MTR Database Manager in collaboration with the CSS/WSCR Database Manager. In order for the MTR Database Manager to perform the matching, the tumor registries will provide the MTR Database Manager with access to a data file containing all breast cancer cases in the registry, produced at regular intervals (e.g. monthly) or upon request.

b. Description of the recruitment process.

All facility participation is voluntary. Mailings describing the MTR and study results are regularly provided to all 179 radiology facilities in Washington State. Facilities interested in participating in the MTR discuss participation with study investigators and staff. Participating facilities will agree to use the data provided by the MTR for quality assurance/improvement activities and not use the data for marketing. A data release agreement (see attached agreement) will be signed by all facilities and will identify the individual at each facility who is responsible for receiving MTR reports.

Figure 1. Overview of MTR Linking Process



c. Description of the Informed Consent Process

Radiologist Participation

Background: One result of linking individual mammography outcomes with cancer diagnosis data contained in the CSS and WSCR is the identification of patients who have been diagnosed with breast cancer after having a mammogram interpreted as negative or benign. Although it is possible for radiologists to track mammograms, which have been interpreted as negative or benign by requesting

follow-up information, or by making arrangements with local tumor registrars to routinely identify breast cancer cases among their patients, these approaches are not reliable and are prohibitively expensive.

Reporting of Data: A radiologist report, which contains patient-identified information may be made available to a requesting radiologist (Individual) or radiology group (Group). Each report will contain only information germane to the requesting individual physician or group of physicians. A radiologist may request a report containing information about only his/her patients. Similarly a group of physicians may request data only for radiologists who currently interpret mammograms for that radiology group. The radiologists and the facility will not be named on the report, but will be identifiable by codes. A second member of the MTR staff will verify the codes to ensure that the correct report is sent to the proper recipients. The recipient will be instructed not to file this report in any permanent record associated with any individual.

Request for Data: The patient-identified-radiologist-level report is provided upon written request by a physician or group. A card has been prepared to send to eligible physicians and a sample letter is available for groups, which wish to have the information combined and sent to one designated recipient (see attached sample letter). This letter must include the following: 1) the purpose for requesting the data; 2) the name and position of the person designated to receive the data; 3) a statement acknowledging his/her ethical and legal responsibility to protect the confidentiality of the data according to Washington State Law; 4) an indication that the data will not be used for any purpose other than quality improvement; 5) an agreement that no patient will be contacted as a result of receiving the data. In addition, a request from a radiology group must include two additional items: 6) names of the radiologists of record whose patients are to be identified and 7) a statement from the designated recipient that he/she is authorized by each of the radiologists of record to receive the data.

Datasets created for research purposes from the MTR database are stripped of patient-identifiers. However, in order to provide patient-identified reports, separate datasets containing patient-identifiers will be maintained. All MTR datasets are stored electronically on password-protected computer systems. At the request of a participating physician or institution, the MTR Database Manager will generate a radiologist level report (see attached report) containing patient-identified breast cancer data linked to mammography data. A cover letter will accompany this report stating that the report should not be filed in a permanent record. A manual quality control check will be performed on a randomly selected sample of the data contained in the report to ensure the accuracy of the patient identifiers, cancer data, radiologist of record and the institution where the mammogram was performed. A paper copy of the report will be printed, reviewed by the Principal Investigator, and sent directly to the individual physician or designated physician who requested the report. Patient or Physician-identified MTR data will not be distributed to any other party or published in any form. The report will not be stored permanently at FHCRC in either paper or electronic form. The CSS/WSCR Pledge of Confidentiality and the MTR Pledge of Confidentiality will be strictly adhered to at all times.

Mammography Patient Participation

Informed consent for each individual exam is not currently obtained because the risk of disclosure of patient identified-information (the only risk of this study) is minimal compared to the anxiety and potential harm caused by requiring individual informed consent and the impracticality due to administrative and cost implications for the radiology facility.

This does not have any direct patient contact, and uses data currently collected by radiology clinics. All research activities involve the use of aggregated audit outcome only. Exclusion of any study subject would potentially invalidate the audit measures. Individual patient data is maintained for administrative and linkage purposes only and is removed prior to any research activity. No patient is contacted for any reason due to their inclusion in the electronic data provided by the radiology facility. Procedures

describing the informed consent process are described below. All data for both women and physicians are protected by a Federal Certificate of Confidentiality also described below.

Attachments

1.2	MTR Data Validation and Linkage Protocol
2.1	CSS/WSCR Confidentiality Pledge
3.2	MTR Confidentiality Pledge
3.3	Certificate of Confidentiality
4.1	Facility Confidentiality Agreement/Data Release
5.3a	Individual Radiologist request for patient-identified report
5.3b	Group/Head Radiologist request for patient-identified report
5.5	Radiologist/patient-identified report

d. Subject assignment (randomization). This is an observational study with no randomization of subjects.

e. Evaluation prior to entry. There are no exclusions to entry, all available data from participating radiology clinics is utilized.

f. Evaluations. There are no direct subject evaluations as part of the registry aspect of this study.

g. Clinical assessments. There is no direct patient contact and therefore there are no clinical assessments planned as part of this study.

h. Describe the research intervention or activity that the subject will experience. There is no direct patient contact involved in this study.

9. Risks/Benefits Assessment.

a. Describe risks associated with the research, measures to be taken to minimize and/or eliminate risks.

The key risk to the radiologists and patient subjects involved in this study is disclosure of information. For radiologists the risk is disclosure of performance information and for patients the risk is disclosure of medical history information. This risk is minimized by ensuring that identified data is accessed by only the database manager and no other study personnel or investigators. Detailed data handling procedures are followed for the database manager and all study staff.

In order to guarantee that a patient's medical history will at all times remain confidential the following precautions will be taken by the MTR. As it is essential that patient-identified information is released only to a physician or group that has treated that patient, the MTR will follow the same procedures as CSS for tracking a physician or institution. Each mammogram contained in the MTR database has been assigned a code in the "Radiologist of Record" field, which identifies the radiologist who interpreted the mammogram. Also, a code for the institution, which provided the data, will be tracked with each mammogram. Once a report has been generated, these data will be independently verified by the Database Manager to ensure that patient-identified information is released only to entitled physicians and groups.

Cancer data provided by the registries will be used only for purposes related to the maintenance of a linked Mammography Tumor Registry. Cancer data, which are not linked to mammographic data will not be duplicated or distributed for any reason. If the process of linking is discontinued, all non-linked cancer data provided by the registries will be destroyed. A signed CSS/WSCR Pledge of Confidentiality will be signed by MTR investigators and staff and copies will be provided to the IRB and the procedures outlined in the Pledge will be adhered to at all times by MTR investigators and staff.

All reasonable precautions will be taken to ensure the protection of confidential data. Existing CSS confidentiality procedures will be used as the guideline for MTR procedures. Electronic data files exchanged between MTR and the registries will be encrypted with a password using Pkzip software (Pkware, Inc.), and will be transferred on diskette or via private network systems. Diskettes containing confidential data will be stored in locked cabinets when not in use. Data files transferred via a network will be placed in a private directory, which is accessible only to authorized MTR or registry personnel. Access to the directory will require a user ID and a password. Passwords will be communicated in person or by telephone, and will not be stored with the data files. The computers connected to the network will be protected by a two-layered password system. A password will be required to start, or "boot" the computer and a second password will be required to regain access to the computer after a short period of inactivity. Breast cancer data provided by the registries for linking purposes will remain encrypted except while in use during the linking process. The non-encrypted registry data will be deleted from the computer disk immediately after each use. A software utility will be used to ensure that the data cannot be recovered after deletion.

The MTR Pledge of Confidentiality will be signed and adhered to by MTR investigators and staff. A copy of all signed Pledges will be maintained by the MTR and the originals will be forwarded to IRB.

In addition, all data maintained by the MTR is protected from disclosure or subpoena, for any reason by a Certificate of Confidentiality, issued under section 301(d) of the Public Health Service Act by the US Department of Health and Human Services.

b. Describe the benefits of the research to the subject. The primary benefit to participating radiologist subjects is access to detailed audit information regarding outcome of all exams, which is not available through any other outlet. There is no direct benefit to patient subjects other than the potential for improved mammography quality.

c. Payment or compensation. There is no compensation to radiologist or patient subjects.

10. Report of serious or unexpected events.

a. Serious or unexpected adverse events can occur in any and all types of studies, not just experimental interventions or clinical trials.

b. Include a definition of what constitutes an adverse event in the study. An adverse event would be the disclosure of any individually identified confidential radiologist or patient information.

c. Describe agencies or offices to be notified with point of contact information in the event of a serious and unexpected adverse event.

The primary office to be notified is the Fred Hutchinson Cancer Research Center Internal Review Office. Upon any adverse event, Karen Hansen at 206 667-4867 will be notified as soon as possible.

11. Description of Protocol Drugs or Devices. There are no investigational drugs or devices.

12. Disposition of Data. Describe where the data will be stored, who will keep the data, how the data will be stored, and the length of time data will be stored.

Maintenance and storage of all study data will be overseen by the Database Manager. Existing CSS confidentiality procedures will be used as the guideline for MTR procedures. Electronic data files exchanged between MTR and the registries will be encrypted with a password using Pkzip software (Pkware, Inc.), and will be transferred on diskette or via private network systems. Diskettes containing confidential data will be stored in locked cabinets when not in use. Data files transferred via a network will be placed in a private directory, which is accessible only to authorized MTR or registry personnel. Access to the directory will require a user ID and a password. Passwords will be communicated in person or by telephone, and will not be stored with the data files. The computers connected to the network will be protected by a two-layered password system. A password will be required to start, or "boot" the computer and a second password will be required to regain access to the computer after a short period of inactivity. Breast cancer data provided by the registries for linking purposes will remain encrypted except while in use during the linking process. The non-encrypted registry data will be deleted from the computer disk immediately after each use. A software utility will be used to ensure that the data cannot be recovered after deletion. Data will be maintained throughout the funding period and as appropriate based on subsequent funding.

13. Modification of the Protocol. Any modification to the protocol will follow established protocol modification procedures of the FHCRC Internal Review Office and the HSRRB for review and approval, which include detailed submission of any changes or additions.

14. Departure from the Protocol. If the study investigators or staff, become aware of any departure from the protocol, the FHCRC Internal Review Office will be notified in writing as well as the HSRRB office.

15. Roles & Responsibilities of Study Personnel

Nicole Urban, ScD, Principal Investigator (20% FTE). Dr. Urban will be responsible for overall coordination of logistics, facilitation of progress of the scientific teams, and communication at both the investigator and staff level, overall design and conduct of all research activities, and interdisciplinary leadership for the project. Dr. Urban will oversee all aspects associated with the Mammography Tumor Registry and evaluation of mammography performance including manuscript preparation and report generation.

Martin McIntosh, PhD, Statistician (20% FTE). Dr. McIntosh will be responsible for the data that describes the laboratory analyses and for the data analysis relating to the validation of markers that may be added to a breast biomarker panel and will guide the development of the MTR as appropriate. He will work closely with Ms. Guay to develop analysis sets for use by the investigators. He will work with the other investigators to solve methodological problems associated with collected variables and data analysis. Dr. McIntosh will collaborate with Drs. Urban and Anderson in this methodological work. He will also participate in manuscript and report preparation.

Mariann Drucker, MD, Swedish Medical Center Radiologist (5% FTE). Dr. Drucker is a highly experienced mammographer in the Swedish Breast Care Center. She will provide clinical guidance and

expertise to the project about breast cancer screening and will help interpret mammography data. She has been an investigator on the Mammography Tumor Registry (MTR) since 1994 and has served as the liaison to the medical community in Washington State and as the primary contact for radiologists participating in the MTR project. She will supervise interactions between project staff and radiologists and their staff. Dr. Drucker, her associates and their staff, will administer the consent to contact form and Screening Questionnaire to patients and will invite women undergoing stereotactic biopsies to participate. She will work with Drs. Ramsey and Kessler and Ms. McAree to address the clinical utility of the panel of biomarkers. She will attend Investigator and Interdisciplinary Working Group meetings and provide leadership in interpreting the clinical relevance of mammography findings.

Steve Zeliadt, Informatics Manager, (50% FTE). Mr. Zeliadt has managed the Mammography Tumor Registry (MTR) for over six years and will continue to oversee all MTR related activities. In addition, he will be responsible for managing informatics including the Specimen Tracking System (STS), access to and analysis of data, report generation and web-based communication tools (FlexKB). The broad scope of his responsibility will include database design and development, maintenance and updates of the linked mammography tumor registry, design and development of data collection instruments, coordinating investigator requests for analysis datasets, development of standardized reports describing the Specimen Repository, and management of the STS. Mr. Zeliadt will coordinate quarterly data transfers from radiology facilities to the study office and identification of high-risk patients based on mammography and questionnaire data, and linkage of mammography data to the SEER/WSCR registries to identify cancers in the screening population. Mr. Zeliadt will develop task lists and timelines for the database development work, and work with Carole Shaw, the Database Manager, and programmers to ensure that study requirements for informatics support are met. Mr. Zeliadt will serve as liaison with Lauren Clarke, the consultant developing the FlexKB system to support real time inter-institutional communication and project updates between investigators. Mr. Zeliadt will supervise the Database Manager.

Sue Peacock, MS, Statistical Research Associate (50% FTE) Ms. Peacock is a Masters level epidemiologist with experience managing and analyzing large datasets. Ms. Peacock will be responsible for statistical procedures including data quality control, dataset cleaning and analysis for all study data. She will work closely with Drs. McIntosh and Anderson to evaluate the results of surveys and questionnaires, and will provide statistical analysis support to study investigators.

Carole Shaw, Database Manager (50% FTE) Ms. Shaw currently has responsibility for two databases which will be used for the study: the linked mammography tumor registry, and the STS which is used to track inventory and laboratory results for biological specimens for the ovarian SPORE. Ms. Shaw will continue to manage and oversee all database activities. She will develop a study database to identify all subjects who have agreed to participate and routines to select and identify eligible participants. Other features of the database will include reports documenting the status of participants and generation of follow-up letters for serial blood draws. She will analyze the current specimen tracking system and develop revised software design specifications necessary for this study and a plan for porting existing data in the legacy system to the new data structure. She will be responsible for ongoing database design and management, including data collection, data validation, and quality assurance checks on the linkage process as the database becomes more complex. She will be responsible for resolving disparity among linked data items, and for ensuring confidentiality. Ms. Shaw will make any adaptations to the STS to ensure that it meets the needs of this study, and for development of reports documenting the status of specimens collected for the study, including inventory, tracking, and laboratory value reporting. Ms. Shaw will be the primary contact for data management personnel for the exchange of data between participating laboratories and mammography facilities.

Paul Maier, CSS System Analyst (5% FTE). Mr. Maier will be responsible for ensuring that the cancer datasets provided by SEER registry are updated and error-free. He will assist Ms. Shaw and Ms. Hager in problem solving and file linking from diverse data systems to ensure all data collected can be utilized.

Mary Baker, CSS System Coordinator (10% FTE). Ms. Baker will assist in interpreting the cancer data from the SEER and WSCR cancer registries. The CSS routinely collects pathology reports on patients with cancer and has established relationships with pathology laboratories. Ms. Baker is familiar with the referral patterns of local pathology laboratories for the performance of estrogen and progesterone receptor assays, HER2, p53 and other markers. Ms. Baker will assist Ms. Gough in obtaining pathology reports for patients who develop cancer and associated reports on estrogen and progesterone receptor assays, HER2, p53 and other markers if they are not performed at the initial laboratory. She will provide for quality control activities, including error checks and other monitoring and surveillance, and will attend project meetings as necessary.

Appendix B
Clinical/Recruitment Protocol

Center for the Evaluation of Biomarkers for Early Detection of Breast Cancer

Funded by the Department of Defense as a Breast Cancer Center of Excellence
Award Number: DAMD 17-02-1-0691
proposal Number: BC013002

Recruitment and Specimen Collection Protocol (IR#5317)

1. **Protocol Title**: Breast Cancer Early Discovery Study

2. **Phase.** Not applicable

3. **Principal Investigator**: Nicole Urban, ScD
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Other Investigators:

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Scott Ramsey, MD, PhD FHCRC 1100 Fairview Avenue North, MP-900 P.O. Box 19024 Seattle, WA 98109 206-667-7846	Meg Mandelson, PhD Group Health Cooperative Center for Health Studies 1730 Minor Avenue Suite 1600 Seattle, WA 98101 206-287-2900	Larry Kessler ScD FHCRC 1100 Fairview Avenue North, MP-900 P.O. Box 19024 Seattle, WA 98109 206-667-6808
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Michel Schummer, PhD MacroGenics 1441 N 34th St Seattle, WA 98103 206-732-1430	Ingegerd Hellstrom, MD, PhD Pacific NW Research Institute 720 Broadway Seattle, WA 98122 206-726-1209	Gordon Mills, MD, PhD MD Anderson Cancer Center 1515 Holcombe Blvd. Houston, TX 77030-4095 713-792-2121

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Medical Monitor: This study has been determined to be minimal risk by the Department of Defense Human Subject Reviewer, so identification of a medical monitor is not necessary.

4. Locations of Study:

Fred Hutchinson Cancer Research Center 1100 Fairview Avenue North, MP-900 P. O. Box 19024 Seattle, WA 98109	University of Washington (Kiviat Laboratory) Harborview Medical Center Dept. of Pathology Box 359791 325 Ninth Ave. Seattle, WA 98104
Group Health Cooperative Center for Health Studies 1730 Minor Avenue Suite 1600 Seattle, WA 98101	PhenoPath Laboratories 3000 First Avenue #1 Seattle, WA 98121
Virginia Mason Research Center 1201 Ninth Ave. Seattle, WA 98101	MacroGenics 1441 N 34th St Seattle, WA 98103
Pacific Northwest Research Institute 720 Broadway Seattle, WA 98122	University of Texas MD Anderson Cancer Center 1515 Holcombe Blvd. Houston, TX 77030-4095
University of Washington Medical Center 1959 N.E. Pacific Seattle, Washington 98195	University of California Los Angeles Cedars-Sinai Medical Center, #160-W Los Angeles, CA 90048-0750

Swedish Medical Center Breast Care Center Dr. Dwyer (Radiologist) Dr. Stracener (Radiologist) 1101 Madison St., Suite 310 Seattle, WA 98104	Swedish Medical Center Drs. Hart, Florence and Horton (Breast Surgeons) Arnold Pavilion 1221 Madison, Suite 1411 Seattle, WA 98104-1360
PacMed Clinics Dr. Needle (Breast Surgeon) 1200 12th Avenue South Seattle, WA 98144	

5. Expected Start and Completion Dates: 10/1/2002-9/30/2006

6. Purpose and Objectives:

Purpose. The purpose of the Center is to assemble the team and the infrastructure needed to accelerate progress in breast cancer early detection biomarker research. We will develop a unique resource for inter-institutional collaborative breast biomarker research, and evaluate the potential of biomarkers detectable in serum or plasma to improve existing breast cancer early detection strategies. We will use the resource to evaluate the performance of candidate breast cancer biomarkers in a cohort of women participating in mammography.

Our vision is that a simple blood test could be used in conjunction with mammography to detect all breast cancer early in the disease process. For example, one clinical scenario might work as follows: at the time of her annual physician visit, a woman could have her blood drawn and tested for a panel of breast cancer markers. If the mammogram were clearly positive, she would be referred for biopsy. If the mammogram were equivocal, she would be referred to biopsy only if the marker panel suggested a malignancy. If the mammogram was negative, but the marker panel suggested malignancy, she would be referred for additional imaging such as MRI. Other scenarios may be preferable, and indeed one of the purposes of our study is to explore other possibilities. For example, use of the marker panel between annual mammograms might identify women with fast-growing tumors.

The expected result of the proposed Center is a panel of markers and decision rules for its use. The panel will be useful clinically, to improve the performance of mammography. Our comprehensive approach and access to an appropriate specimen repository increases the probability of our success. The systematic evaluation of biomarkers for early detection requires access to large numbers of high-quality blood samples. Cases and disease-free women are needed to evaluate the markers' ability to distinguish malignant from healthy individuals. In cases, it is critical that blood samples are obtained prior to treatment of any kind, including surgery, because treatment is likely to affect marker levels. Serial specimens obtained from healthy women are needed to evaluate the variance in marker levels within individual women over time (i.e. intraclass correlation), to establish criteria for marker positivity. Specimens from women representing the range of diagnoses (histology, grade, stage) are needed to assure the marker panel is sensitive to all disease types. Blood samples must be collected, processed and stored identically, as some assays are sensitive to these parameters. Because high-quality specimens are frequently not available, investigators often rely on samples that were obtained from different sources for cases and healthy women. They may have been obtained during remission or even during treatment, or processed and stored differently in ways that affect marker levels. As a result, many markers that appear initially to be very promising prove later not to be

useful, and the development process is characterized by false starts and missed opportunities. The scientific community is often skeptical about the claims made for new markers, in part because many initially promising results cannot be replicated in different laboratories.

Another barrier is the clinical challenge we will face if we are successful. Markers could be ordered before, at the same time as, or after a mammogram, by the primary care physician, a radiologist, or the specialist who evaluates suspicious findings. Each strategy will affect the sensitivity and specificity of the combination of tests. If markers identify cancers that cannot be seen on a mammogram, clinical work up to identify the location of the tumor will be required. Cost-effective strategies will be needed. As we will obtain serum for women in several stages of evaluation—prior to screening, just prior to biopsy, and just prior to surgery—we will be in a unique position to evaluate the clinical utility of markers at all these potential stages of screening.

Objectives. Our goal is to evaluate breast cancer biomarkers for their contribution to early detection of breast cancer. Subsets of breast cancer that are missed by mammography, or that grow too quickly to be detected in early stage by annual mammography, are of particular interest. Our aims are:

1. To validate and refine the ability of candidate biomarkers to predict disease status;
2. To evaluate panels of biomarkers for use as an adjunct to mammography, to detect all breast cancer at a highly curable stage; and
3. To identify the molecular signatures of subsets of in situ and invasive breast cancers and explore their associations with biomarkers in the panel.

To support the research goals we will build a unique resource for multidisciplinary, inter-institutional research on breast cancer biomarkers including

1. Blood samples obtained annually and processed identically in women with and without breast cancer,
2. Fresh tissue matched to blood samples on a subset of the women with breast cancer,
3. Epidemiological, clinical and follow-up information for women who donate specimens, and
4. A system to facilitate use of the specimens, including state-of-the-art information systems.

We will develop a specimen resource from a well-characterized population, with associated risk factor information, mammography findings and follow-up data on cancer outcomes. It will include blood samples obtained from selected women who have mammograms, biopsy or breast cancer surgery over the 4-year period of the grant. We will evaluate candidate biomarkers for their ability to distinguish among women with healthy breasts and women with various breast conditions, including invasive ductal and lobular carcinoma, lobular carcinoma in situ, comedo- and noncomedo-type DCIS, hyperplasia and other potentially premalignant conditions, and benign conditions. We will evaluate the role of biomarkers detectable in serum or plasma in improving our current breast cancer early detection strategies.

For selected women, we will explore the feasibility of collection and analysis of fresh-frozen tissue in order to characterize malignant conditions at the molecular level. This will allow us to correlate biomarkers included in the panel with subsets of breast tumors identified through molecular profiling.

Our hypotheses are:

(a) Used alone, biomarkers detectable in blood products can detect subsets of, but not all, breast cancer;

(b) Use of a breast cancer biomarker panel can improve the performance of mammography in early detection of breast cancer.

7. Study Population.

The study population includes three cohorts defined by recruitment source. The first is the approximately 8,600 women who obtain mammograms and undergo biopsies at the Swedish Medical Center Breast Care Center each year. All women seen for mammography at Swedish Breast Care Center (SBCC) will be asked sign a **Consent to be Contacted for Future Research Studies** for potential participation in breast cancer research. The Consent to be Contacted form provides permission for the research study to maintain the woman's name and contact information indefinitely so that she may be invited to future studies. Risk factor information will be collected from women who consent to be contacted using the **Cancer Research Registry Questionnaire**. Within 3 months following the mammogram, data describing mammogram findings will be submitted to FHCRC in accordance with Mammography Tumor Registry procedures (FHCRC IR#3636). For women undergoing mammograms, mammogram findings (assessment codes, follow-up recommendation, breast density) and data from the Cancer Research Registry Questionnaire will be used to classify women with respect to risk status. A stratified random sample of these women will be identified and asked to provide blood samples annually at the time of subsequent mammograms. Women at high risk will be over-sampled to increase the expected number of women with sequential blood samples obtained prior to a breast cancer diagnosis. As shown in Table 1, 500 (375 high-risk and 125 average-risk) women will be enrolled in Year 1, and 100 additional women will be enrolled in subsequent years. In addition, all women undergoing biopsies will be invited to provide a blood specimen prior to biopsy and annually at the time of subsequent mammograms. 100 women undergoing biopsies will be enrolled annually. Women identified and enrolled through the SBCC, including women having both mammograms and biopsies, are referred to as the Mammography Cohort (MC).

The second cohort includes women undergoing breast surgery at Swedish Medical Center. The second recruitment source is the approximately 650 women who have surgery for breast cancer at SMC each year. Collaborating surgeons will identify those most likely to have tumors of size > 2 cm and therefore to be candidates for tissue collection. In 1999 there were 124 women who had surgery for breast tumors over 2 cm at SMC. These women will be sampled with probability 1. Remaining women will be sampled with lower probability to yield desired numbers in the cohort. Based on our experience in the ovarian SPORE, we expect that tissue collection will occur in about 50% of the women sampled. As shown in Table 1, we expect to enroll 25 women in Year 1 and 50 women annually thereafter for donation of both blood and tissue. Fresh tissue specimens will be obtained when it is logistically and ethically appropriate. In addition we expect to enroll 100 women annually beginning in year 2 for donation of blood only. Blood samples will be obtained just prior to or at the time of the surgical procedure. Women identified and enrolled through our collaborations with SMC surgeons are referred to as the Surgical Cohort (SC). Following surgery and treatment, women in the SC will be invited to participate in the MC, providing blood samples at the time of their annual mammograms.

The third recruitment source is women undergoing biopsy by Mammotome® at Cedars Sinai Hospital. Approximately 2,500 women undergo this procedure annually. Of these we will enroll 50 per year, including women with benign lesions, hyperplasia, and in situ disease as well as women with invasive carcinoma. As at SMC, we expect about 20% to be malignant. Both fresh-frozen tissue and blood samples will be donated by women in the Cedars biopsy cohort. Cedars

Sinai has an established protocol to collect specimens from individuals undergoing breast surgery (see item 5). This is a broad protocol that is intended to collect specimens for multiple breast cancer studies and the Cedars breast tissue bank. Because it is a general protocol, the scientific objectives and eligibility criteria for the Cedars protocol are broader than for the Breast Cancer Early Discovery Study. However, specimens collected under the Cedars protocol may be released to FHCRC for selected patients who meet the eligibility criteria for the Breast Cancer Early Discovery Study. Page 5 of the Cedars protocol describes the formal process required to release specimens. This process will be followed for specimens allocated to the Breast Cancer Early Discovery Study.

The Cedars protocol will be revised over time to more closely resemble the Seattle protocol. The next step will be to include Breast Cancer Early Discovery Study data collection instruments in the Cedars protocol. We will obtain additional IR approvals to collect selected data needed for Aim #3 from Cedars patients participating in the study. We will forward the updated Cedars documentation as soon as possible.

Table 1. Unique Participants

	Yr 01	Yr 02	Yr 03	Yr 04	Total
Mammography Cohort – High Risk	375	75	75	75	**600**
Mammography Cohort – Average Risk	125	25	25	25	**200**
Mammography Cohort – Biopsy	100	100	100	100	**400**
Subtotal: Mammography Cohort	*600*	*200*	*200*	*200*	***1200***
SMC Surgical Cohort: Blood and Tissue	25	50	50	50	**175**
SMC Surgical Cohort: Blood Only+		100	100	100	**300**
Subtotal: Surgical Cohort	**25**	**150**	**150**	**150**	**475**
Cedars Biopsy Cohort: Blood and Tissue	50	50	50	50	**200**
Total	**675**	**400**	**400**	**400**	**1875**

8. Protocol Design. This protocol outlines the methods for a study to collect blood and tissue specimens from women undergoing mammography and breast-related biopsy and surgery at Swedish Medical Center. Patient approach procedures to be used at Cedars Sinai Medical Center are addressed in a separate, attached document. The study uses the already-established infrastructure in place for the Mammography Tumor Registry Study (MTR). The purpose of the study is to provide a specimen resource to support both breast and ovarian cancer biomarker evaluation. Investigators propose to build a unique resource for multidisciplinary, inter-institutional research on cancer biomarkers including blood samples obtained annually and processed identically in women with and without breast cancer, fresh tissue matched to blood samples on a subset of the women with breast cancer, epidemiological, clinical and follow-up information for women who donate specimens, and a system to facilitate use of the specimens, including state-of-the-art information systems. Collaboration with mammography facilities and surgeons offices is planned to recruit women undergoing screening, biopsy and surgery.

8a. Eligibility Criteria. All women 18+ years of age undergoing mammography or biopsy at the SBCC are potential participants for this research. Women identified and enrolled through the SBCC, including women having both mammograms and biopsies, are referred to as the Mammography Cohort (MC). All women 18+ years of age scheduled for breast surgery by participating surgeons are potential participants for this research. These women are referred to as the surgical cohort (SC).

Mammography Cohort Risk Stratification. Women having screening mammograms will be invited to complete the Cancer Research Registry Questionnaire. Of those who respond, study investigators will select a stratified random sample and invite those women to donate blood. Risk stratification will be based on epidemiological data provided on the questionnaire, and on mammogram findings, as follows:

- A woman will be considered average risk if her mammogram result was assessment code 1 or 2.
- Women will be classified as high risk if:
    1. she is referred to biopsy (assessment code 4 or 5); or
    2. she has two or more first degree relatives who have been diagnosed with breast and/or ovarian cancer; or
    3. she presents with suspicious mammogram findings (assessment code 3), has experienced symptoms, and information gathered from the Gail model indicates that she is high risk for breast cancer.

8b. Subject Identification. Potential participants in this study will be identified at the Swedish Medical Center Breast Care Center (SBCC). This mammography practice already participates in the Mammography Tumor Registry (IR File #3636), which means they provide regular downloads of mammography data that are routinely linked to the Cancer Surveillance System. The registry is used to support breast cancer research and to provide regular performance reports to participating radiologists. All aspects of the linkage process, including extensive confidentiality procedures, are covered in IR file #3636 and are not discussed here.

8c. Participant Approach, Enrollment, Informed Consent and Specimen Collection. Approach processes are tailored to participant type. All women receiving screening mammograms are asked to sign a consent for future contact. Women receiving biopsies are approached prior to the biopsy procedure. Women in the surgical cohort are approached at the pre-surgery appointment. All women who consent to participate in the initial blood collection are invited to donate blood at their subsequent mammogram appointment (regardless of cohort).

8c.1 Consent to Contact (Mammography Cohort). All women seen for mammography at SBCC will be asked to sign a **Consent to be Contacted for Future Research Studies** for potential participation in breast cancer research. Additional risk factor information will be collected using the **Cancer Research Registry Questionnaire**, which will be mailed to the participant after she completed the Consent to be Contacted. This mailing will also include a HIPAA compliant medical records release, which will allow access to her mammography records. Within 3 months following the mammogram, data describing mammogram findings will be submitted to FHCRC in accordance with MTR procedures. For women undergoing mammograms, data from the SBCC's routine patient questionnaires, and data from the **Cancer Research Registry Questionnaire** in combination with mammogram findings (assessment codes, follow-up recommendation, breast density) will be used to classify women with respect to risk status. A stratified random sample of these women will be invited to donate blood.

8c.2 Invitation Letter and Consent for Annual Blood Donation (Mammography Cohort) Women selected for approach will be contacted by mail several months prior to the next mammogram appointment, using the **Invitation Letter**. The letter will describe the study and invite interested women to return a signed **Consent for Data Collection and Blood Donation** and a **Medical Records Release Form.** Upon receipt of the signed consent form, a blood collection packet and **Baseline Questionnaire** will be mailed to the participant, who will be invited to undergo her blood draw at a Dynacare clinic across the hall from the Breast Center or at the Marsha Rivkin Center on the SMC campus just *prior* to her next mammogram. If a woman

does not return the consent form and Baseline Questionnaire after two weeks, then the study office will place a follow-up call. If the woman verbally declines the invitation to participate in this study, then the staff person will complete a **response sheet** detailing why the woman has declined the invitation. The study staff will prepare and deliver blood kits to the Dynacare Clinic near SBCC, as well as to SBCC to be used for this study. Each woman will be asked to complete an initial **Health Status Questionnaire** just before or after her first blood draw. In subsequent years, each participant will be sent a **Reminder Letter** along with a **Health Status Update** questionnaire.

8c.3 Telephone and In-Person Approach (Women Undergoing Biopsy) All women undergoing biopsies will be invited to provide a blood specimen prior to biopsy and annually at the time of subsequent mammograms. Consent for specimen donation will take place during the biopsy appointment, prior to the biopsy. The SBCC Scheduling Nurse routinely contacts by telephone all women undergoing stereotactic or in some cases ultrasound-guided biopsy 2-3 days prior to the appointment. During this phone call, the scheduling nurse will obtain verbal consent for the study Research Nurse to contact the woman by phone to discuss study participation. If a woman provides verbal consent, the SBCC nurse will fax the study office the **Biopsy Flowsheet** including the woman's name and the date and time of the biopsy appointment to the confidential fax at the study office. The Research Nurse will then telephone the participant to describe the study and obtain verbal consent to attend the biopsy appointment. This telephone contact will generally occur 2-3 days before the biopsy appointment, and a minimum of one day before the appointment.

Only-women undergoing pre-scheduled stereotactic or ultrasound guided biopsies will be approached to participate in this study. Women undergoing a biopsy on the same day as a suspicious mammogram will not be approached for the study.

In all cases where the Research Nurse attends the biopsy appointment, she will discuss what is involved in study participation and encourage the woman to ask any questions she may have about participation, and to discuss participation with any family members who are present. The consent process will take place in a private consultation or examination room in the breast care center. Clinical staff at the SBCC will serve as witnesses to the informed consent process. If the woman decides to participate, the Research Nurse will obtain written informed consent for the blood donation using the **Consent for Data Collection and Blood Donation Prior to Biopsy** and draw blood from the participant *prior* to the procedure. Blood is drawn prior to the procedure to ensure that marker measurement is not affected by any inflammation associated with the procedure, and also for convenience to the participant so that no additional time and travel are required for participation. The participant will also be asked to sign a **Medical Records Release Form**. A copy of both the consent form and the medical records release form will be provided to the participant. If the Research Nurse is not immediately available, the informed consent and blood draw procedures may be conducted by the SBCC nurse. Participants will be asked to complete a **Health Status Questionnaire** either just before or just after their first blood draw. All consented participants will be provided the **Baseline Questionnaire** which they may complete immediately or to return later by mail. These women will also be asked to provide blood specimens annually with their subsequent mammograms, regardless of the outcome of their biopsy, using the Reminder Letter as described in Section 4.2. At each subsequent draw they will also be asked to complete the **Health Status Update**.

8c.4 Approach via Breast Surgeons (Surgical Cohort). Several breast surgeons at Swedish Medical Center have agreed to identify patients that are likely candidates for surgical specimen collection. Women selected for approach based on the surgical schedule will be approached at the pre-surgical appointment for consent to obtain specimens. The informed consent will be

conducted by a study Specimen Collection Specialist (SCS) or the Research Nurse. Women will be asked to sign a **Consent for Data Collection and Specimen Donation At Surgery** allowing permission to obtain a blood sample *prior* to surgery, and to donation of breast cancer tissue should there be excess tissue available. Women will also be asked to sign a **Medical Records Release Form**, which allows researchers to access their surgical pathology report and other records related to their cancer diagnosis. This is the procedure that we have used successfully to obtain blood samples and tissue from women undergoing surgery for suspected ovarian cancer at SMC. We will obtain also consent to obtain tissue blocks, which are stored for 10 years at SMC and made available routinely to investigators at the FHCRC.

8c.5 Specimen Collection and Processing

8c.5.1 Blood Collection. In all blood collections, the phlebotomist will use a vacutainer and 21 ga needle to collect up to 50 ml of whole blood in three 10 ml (red top) tubes and two potassium EDTA 10 ml (purple top) tubes. The volume of blood drawn may be adjusted downward as necessary if a clinical draw is also being conducted the same day. On selected participants, one 10 ml potassium EDTA tube will be transferred to the Kiviat laboratory for processing, as described below. The remaining four tubes will be processed into serum and plasma at Dynacare's central processing facility. Samples will be prepared and frozen as quickly as possible, within 4 hours of collection. Blood specimens will be stored in very small quantities to avoid freeze-thaw cycles and re-aliquotting. Times of blood draw, processing and freezing will be recorded. On selected samples, including all women for whom fresh tissue is collected, the Kiviat laboratory will process one 10 ml potassium EDTA tube into plasma and white blood cell pellets for studies of RNA, DNA and protein.

8c.5.2 Tissue Collection A log of scheduled surgeries for potential tissue donors will be maintained so that the SCS can be present at the surgery. Immediately after the surgeon has removed the necessary tissue and the pathologist has taken what is required for pathologic diagnosis, the SCS will be permitted to collect specimens from the removed tissue for the purposes of the study.

For each scheduled surgical specimen collection, a packet containing the specimen collection and processing forms, and a copy of the informed consent form, will be assembled and provided to the Specimen Collection Specialist (SCS) with the scheduled surgery report. The specialist will use a pre-assembled specimen collection kit for tissue and blood collection. The TCS will coordinate with the laboratory personnel to order, maintain, and assemble supplies for the specimen collection kit. The specimen collection kit will include the following pre-labeled items:

- Biohazard bags (with foil and cassettes) for snap frozen tissue specimens
- One (1) truncated embedding mold for primary tumor/tissue specimens frozen in OCT compound
- Three (3) 15 ml. formalin jars for fixed specimens
- One (1) STM tube for primary tumor tissue
- Two (2) 5 ml. lavender-top EDTA tubes for blood collection
- Three (3) 10 ml. red-top tubes for blood collection
- Ten pre-labeled cryovials for serum processing
- Dry ice
- Biohazard stickers and dry ice labels
- Specimen transmittal form

Frozen Tissue Amounts and Preparation:

- It is anticipated that only a very small amount of tissue will be available to the study. Whatever tissue is available will be divided into approximately 1 cm^3 sections. Each section will be completely wrapped in aluminum foil and immersed in liquid nitrogen for a minimum of 3 minutes.
- Frozen tissues will then be placed in tissue cassettes pre-labeled with the specimen identification number using a SECURLINE permanent marker.
- Snap frozen tissue specimens will be stored in the liquid nitrogen thermos for transport to the Kiviat laboratory.
- For the OCT mold, truncated molds will be pre-labeled with the UPN using a SECURLINE permanent marker.
- Each mold will be partially filled with OCT medium and pre-cooled by holding over (not in) liquid nitrogen until OCT medium loses transparency.
- Approximately 1 gm of tissue will be placed in the mold, covered with OCT medium and immersed into liquid nitrogen until completely solid.
- OCT Specimens will be placed into a UPN labeled biohazard bags and stored on dry ice for transport to the core facility.

Paraformaldehyde-Fixed Tissue Amounts and Preparation:

- A portion of tumor smaller than or equal to 1x1 cm and no thicker than 2 mm will be selected and placed in cold 4% paraformaldehyde and stored for 2 hours at 4°C.
- After a 2-hour fixation, the 4% paraformaldehyde will be discarded and replaced with cold 30% sucrose, and the sample will be stored at 4°C.
- Tissue will initially float in sucrose but when left overnight will sink.
- After the tissue has sunk, but no longer that 24 hours after fixation, the tissue will be imbedded in OCT as described in protocol for tissue preparation. (see above)
- The mold will be placed into a labeled biohazard bag and stored at -70° C until transfer to the liquid nitrogen freezer at the Kiviat laboratory/repository.

8c5.3 Specimen characterization. For all cases with fresh tissue, Dr. Kiviat will perform histology review.

8c.5.4 Specimen Storage. Each specimen will be labeled with a unique 6-digit numeric label. A duplicate of this label is affixed to a specimen transmittal form identifying the specimen type and participant number, and logged into the database. Examples of these specimen transmittal forms are presented as Instruments 9 and 10. Blood specimens will be stored in a -70° C freezer, and tissue specimens will be stored in a liquid nitrogen freezer.

8c.5.5 Repository Quality Control. A rigorous quality assurance plan is already in place that includes monitoring and maintenance checks of equipment, an eight-hour CO2 back-up system and a temperature-sensitive alarm system that alerts the building maintenance staff when the interior temperature reaches a designated temperature.

8c.5.6 Repository Use. A Specimen Review Committee described in the Communication section will oversee use of specimens in the resource. Advocates will participate in this committee.

8d. Subject Assignment (randomization): Not applicable.

8e. Evaluations Prior to Entry. No clinical evaluations are made prior to entry into the study, except that mammogram findings (assessment codes, follow-up recommendation, breast density) are used to classify women with respect to risk. The mammogram findings are obtained

through procedures outlined in the Mammography Tumor Registry (IR#3636). A stratified random sample of women in the mammography cohort are invited to donate blood annually at subsequent mammograms, as described in Section 7.

8f. Evaluations to be made during the conduct of the study. Breast cancer case status will be ascertained on all women using the MTR system of linking to CSS/SEER and Washington State Cancer Registry Data, which include date of diagnosis, stage and grade of disease, histology, age, and race/ethnicity, in addition to individual identifiers. Linkage with high-quality cancer registry data provides passive follow-up for cancer outcomes, including survival. A Certificate of Confidentiality was obtained to protect the linked data from subpoena. These procedures are outlined in detail in IR#3636.

8g. Clinical Assessments. Pathology reports will be obtained routinely for women diagnosed with cancer at SMC to obtain day of diagnosis (CSS records only the month and year) for women in the SC and the subset of women in the MC who have undergone biopsy. This information will be collected using the **Patient Pathology at Diagnosis Form** (currently under development) Additional clinical data will be collected using the **Clinical Status Form** (currently under development).Other data collection instruments include the **Cancer Research Registry Questionnaire**, the **Baseline Questionnaire**, the **Health Status Questionnaire**, the **Health Status Update** which are attached to this protocol.

8g.1 Baseline Questionnaire Reliability and Validity

In an effort to ensure high quality data and to maintain common data elements, investigators have decided to use a Baseline Questionnaire that they are already using in collaborative work in the national Risk of Ovarian Cancer (ROCA) screening trial. Although significant statistical and clinical expertise were involved in questionnaire development, the CGN questionnaire has not been formally tested for validity and reliability. Investigators agree that it is not feasible to assess the validity of the questionnaire because of the substantial personnel effort that would be required to review source documentation such as medical records.

Investigators do plan to plan to assess the reliability of selected measures on the questionnaire, by comparing the responses to variables that are captured on both the Baseline Questionnaire (completed at baseline) to the Health Status Questionnaire (completed at each blood draw). Dr. Garnet Anderson will oversee the design and conduct of a reliability assessment for the Baseline Questionnaire. Dr. Anderson is an investigator at the Women's Health Initiative (WHI) statistical coordinating center, and has significant expertise in this area. WHI investigators have recently completed a study assessing the reliability of selected baseline measures in the WHI Observational Study (Ann Epidemiol 2003; 13:1-15, in press). This study observed that most demographic factors, reproductive variables and family medical history were reliably reported, with kappa or weighted kappa above 0.8. Most of the self-reported medical conditions yielded kappa above 0.75. Investigators anticipate that the Breast Cancer Early Discovery study will observe similar reliability using the Baseline Questionnaire, since many of the measures are the similar to those used in the WHI baseline questionnaires.

8h. Research Intervention/Activity that the Participant will experience

Consent for Contact. Women undergoing mammography will be asked to sign a **Consent to be Contacted for Future Research Studies**, which means that they may be contacted in the future to donate blood for this study, or they may be contacted about other studies for which they are potential candidates. An example of another study that may contact these participants is the Ovarian Cancer Early Detection Study, which is recruiting high-risk women to participate in an ovarian cancer screening protocol (IR file #5159).

Screening Questionnaire. To ensure consistency in data collection across sites, the **Cancer Research Registry Questionnaire** will be used at all locations, including the SBCC. This one-page screening questionnaire is used to collect preliminary medical and family history data. A copy of the questionnaire, along with a HIPAA compliant Medical Records Release will be mailed to women after they return the Consent to be Contacted for Future Research Studies.

Annual Blood Donation. Selected women among those who have undergone screening mammography and consented for future contact will approached and requested to donate blood at the time of their next annual mammogram and annually thereafter. Women will be approached and consented by mail, as described in section **8c.2**. Women who donate blood during biopsy, and well as those in the surgical cohort will also be invited to donate blood annually at the time of subsequent mammograms. All women who donate blood will be asked to complete a **Health Status Questionnaire** at the time of their first blood draw, and a **Health Status Update** at each subsequent draw.

Blood Donation at the Time of Biopsy. Women undergoing biopsy at SBCC will be asked to donate blood specimens at the time of the biopsy. They will also donate blood annually thereafter, at the time of subsequent mammograms.

Blood and Tissue Donation at the Time of Surgery. Women undergoing breast surgery will be invited to donate blood and tissue during surgery. Fresh tissue specimens will be obtained when it is logistically and ethically appropriate. Blood samples will be obtained just prior to or at the time of the surgical procedure. They will also donate blood annually thereafter, at the time of subsequent mammograms.

9. Risk/Benefit Assessment

The results of this research will be used to develop ways to find breast cancer early. Specifically, the study aims to develop a panel of biomarkers than can be used in conjunction with mammography to improve its performance. Although there is no direct benefit to women participating in this study, there may be benefits for other women in the future who are at risk for breast cancer or who are living with breast cancer.

Risks to participants including the potential of feeling uncomfortable due to answering personal questions on study questionnaires. Risks associated with blood draw include the possibility of temporary discomfort or a bruise at the site of the needle puncture. Donation of blood and tissue during surgery will not present any additional risks.

10. Reporting of Serious or Unexpected Adverse Events

Adverse events are expected to be rare on this study. Study personnel will have direct exposure to participants only for a short period of time (eg during the consent and specimen collection process), and will not be monitoring participant's health as they would for a clinical treatment protocol. Therefore, study participants will be asked to report any adverse events that they experience that appear to be related to study participation. This will be done by calling the Research Nurse at 206-215-6209 or 1-800-328-1124.

An adverse event is any event that occurs during the study, which results in the subject experiencing a new symptom or worsening of an existing symptom. For example, fainting or loss of cognitive function after a blood draw would be considered an adverse event.

A serious adverse event is an event that results in any of the following outcomes:
1. Death
2. Life threatening event
3. Inpatient hospitalization*
4. Persistent or significant disability or incapacity

**Patients undergoing surgery for breast cancer will be approached to donate blood and tissue for the study. Hospitalization associated with this already-planned surgery will not be considered an adverse event.*

Adverse events will be reported to the FHCRC Institutional Review Office (IRO) at the time of annual review for the study. Adverse events that are both serious and unexpected will be immediately (upon the study office notified) reported by telephone to the FHCRC IRO and by telephone to the USAMRMC, Deputy for Regulatory Compliance and Quality (301-619-2165; FAX 301-619-7803). A written report will follow the initial telephone call within 3 working days. The written report will be addressed to:

U.S. Army Medical Research and Materiel Command
ATTN: MCMR-RCQ
504 Scott Street
Fort Detrick, Maryland 21702-5012

11. Description of Protocol Drugs or Devices: Not applicable.

12. Disposition of Data. All participant materials such as survey responses will be kept in locked cabinets and accessed only by study personnel who have signed a confidentiality pledge. All data will be reported in aggregate format, and will not identify specific participants in any way.

All study materials are stored in locked filing cabinets accessible to study personnel who have signed a confidentiality pledge. All data is stored on a secure network server. Data entry systems are password protected. Access to data files is limited to those study personnel who manage data as part of their job responsibilities and who have signed the confidentiality pledge.

It should be noted that representatives of the U.S. Army Medical Research and Materiel Command are eligible to review research records as a part of their responsibility to protect human subjects in research.

13. Modification of the Protocol. Any modification to the protocol will follow established protocol modification procedure of the FHCRC Internal Review Office and the HSRRB for review and approval, which include detailed submission of any changes or additions.

14. Departure from the Protocol. If the study investigators or staff become aware of any departure from the protocol, the FHCRC Internal Review office will be notified in writing as well as HSRRB office.

15. Roles and Responsibilities of Study Personnel.

Nicole Urban, ScD, Principal Investigator (20% FTE) Dr. Urban will be responsible for overall coordination of logistics, facilitation of progress of the scientific teams, and communication at both the investigator and staff level, overall design and conduct of all research activities, and interdisciplinary leadership for the project. She is currently the Principal Investigator for several interdisciplinary projects involving scientists from molecular biotechnology and clinical immunology disciplines. She will provide the scientific leadership and framework for the evaluation and application of biomarkers for breast cancer screening. Dr. Urban is responsible for coordination of inter-institutional activities, as well as all activities conducted by investigators and staff at FHCRC, including statistical work on development and validation of the marker panel, and coordination of all recruitment, tracking and specimen collection activities. She will work closely with the statisticians and laboratory scientists in carrying out the proposed workplan and ensuring that study objectives are met. Dr. Urban is a recognized leader in interdisciplinary cancer screening research in the Seattle area with the ability to successfully integrate clinical, basic and public health investigators into a unified research team. She will supervise the Project Manager and meet regularly with all Center Investigators to monitor progress and ensure that interim tasks are completed in a timely manner. Dr. Urban will chair the All- Investigator meetings, co-chair the Interdisciplinary Working Group and participate in the Specimen Review Committee.

Judy Nelson, Project Manager (100% FTE) Ms. Nelson will coordinate all activities of the Center at the staff level and supervise the support staff. Ms. Nelson has been the project manager for several clinical studies at the Fred Hutchinson Cancer Research Center involving specimen collection and analysis and has experience managing complex research projects. She will work closely with project investigators to provide overall coordination for the study, and specifically be responsible for managing the relationship between the clinical, laboratory, and statistical components of the study to ensure interim and final deadlines are met. Ms. Nelson will develop timelines with clear deliverables that integrate the activities of the laboratory scientists with the statistical scientists and project leadership. She will coordinate communication between study staff and investigators by soliciting regular written updates from the Informatics Manager and Research Nurse whom she will directly supervise. Ms. Nelson will develop agendas and facilitate staff meetings and investigator meetings. She will provide leadership at the staff level for all study staff, and will directly supervise Nancy Myers, Program Assistant. With the assistance of key staff, Ms. Nelson will compile complete documentation of detailed protocols for participant recruitment and retention, data management, and specimen repository management. Ms. Nelson will oversee all the administrative activities of the study. Ms. Nelson will be responsible for all project management activities such as budget preparation and monitoring, managing logistics of subcontractor relationships, human subjects applications including the necessary cooperative files at subcontractors institutions, facilitating investigator meetings and incorporating investigator decisions into the staff workplan.

Nancy Myers, Program Assistant (100% FTE) will assist the Project Manager in the overall coordination of research activities. She will arrange staff and investigator meetings, prepare minutes, perform literature searches, conduct word processing/desktop publishing of scientific presentations and manuscripts arising from the study, coordinate investigator travel, and provide overall staff support to the project. Ms. Myers will assist with budget monitoring and securing subcontracts in a timely manner. She will be responsible for all purchasing for the study, including office supplies, laboratory supplies and equipment. Ms. Myers will assist the Clinical and Informatics Core staff with participant mailings and data entry as needed.

Advocates

Joan McAree, Advocate (25% FTE) Ms. McAree will coordinate advocate involvement in the research program. She will chair patient advocacy meetings and facilitate ongoing communication among advocates and between the advocate group and study investigators. She will also play a central policy role in evaluating the risks and potential benefits of this research, and in representing her assessment to the Institutional Review Board (IRB). She will attend Institutional Review Board (IRB) meetings when the study is discussed to educate the IRB about the overall goals of the study, and to provide information about patient approach procedures and the confidentiality and privacy protections in place. In addition, Ms. McAree will work closely with Drs. Ramsey, Kessler and Drucker and Ms. Gough to address consideration of the clinical utility of the marker panel. Ms. McAree will attend regular scientific meetings including All-Investigator meetings, Specimen Review Committee meetings, and Interdisciplinary Working Group Meetings. She will represent the research study at local and national advocacy meetings.

Julia Cañas. Julia Cañas will be responsible for coordinating minority recruitment. Ms. Cañas will work through established contacts to disseminate study information and will collaborate with Shin-Ping Tu, a UW investigator responsible for minority recruitment for the ovarian SPORE, to develop culturally appropriate approach protocols for minority populations.

Mona Bailey. Mona Bailey will be responsible for educational outreach. Ms. Bailey will work with Ms. Cañas to develop a study brochure specifically targeting minority groups. She will also coordinate the development and implementation of educational outreach programs geared toward the African American, Asian, and Hispanic communities.

Barbara Bridge. Barbara Bridge will be responsible for development of patient retention materials, and programs to empower breast cancer survivors to be active participants in a research program. Ms. Bridge will work with study investigators and clinical staff on creating survivor-to-survivor letters and reminder cards. She will also coordinate efforts to develop a study brochure and an advocacy newsletter.

Scientists

Martin McIntosh, PhD, Statistician (20% FTE) will be responsible for the data that describes the laboratory analyses and for the data analysis relating to the validation of markers that may be added to a breast biomarker panel. He will work closely with Ms. Guay to develop analysis sets for use by the investigators. He will work with the other investigators to solve methodological problems associated with collected variables and data analysis. Dr. McIntosh will collaborate with Drs. Urban and Anderson in this methodological work. He will also participate in manuscript and report preparation.

Garnet Anderson, PhD, Statistician (10% FTE) Dr. Anderson is responsible for the Patient Registry, including epidemiological, clinical and follow-up information about the women. She will collaborate with Drs. Mandelson and Clarfeld to develop risk assessment and sampling measures that incorporate breast density, mammography outcome, pedigree and other risk factor data, and participate in the development of study questionnaires and other data collection instruments. Dr. Anderson will provide scientific leadership to Shirley Gough in the management of patient contact, data collection and the patient tracking system. She will develop statistical methods for measuring risk using data available from consenting women and associated mammography data. She will work closely with Dr. McIntosh and will coordinate with other investigators in the development and evaluation of potential marker panels resulting from the assays performed on the Panel Validation Set. Together with Dr. Kiviat, Dr. Anderson with co-chair the Specimen Review Committee. Dr. Anderson will participate in manuscript and report preparation.

Nancy Kiviat, MD, Pathologist (10% FTE) Dr. Kiviat will serve as co-PI, responsible for the Specimen Repository. She will be supported by Ms. O'Briant who will manage all activities surrounding specimens from the time of collection to analysis. Dr. Kiviat and Ms. O'Briant will be responsible for specimen inventory control, the specimen tracking system and the Specimen Review Committee. Dr. Kiviat will be responsible for ensuring that the common data elements used to describe stored specimens that are currently being developed by other research networks including SPORE's and the EDRN will be used in this study. She will also be responsible for blood processing protocols and characterization of specimens in the repository. Dr. Kiviat will measure mammaglobin using PCR in DNA from cells obtained from blood. She will work closely with Drs. Schummer and Karlan on methods for extraction, amplification and preservation of mRNA from tissue for molecular profiling work. Dr. Kiviat will also collaborate with Drs. Hellstrom, Mills and Schummer to investigate gene expression in breast tissues. Dr. Kiviat will be responsible for all activities conducted by investigators and staff at the UW. The UW contributes laboratory-based clinical scientists with an understanding of the biology of the disease as well as the needs of the patients. Dr. Kiviat will facilitate communication among the UW laboratory scientists and provide leadership and guidance for the assay development and biomarker measurement activities.

Scott Ramsey, MD, PhD, Health Economist (5% FTE) Dr. Ramsey is an internist and health economist who oversees the Mammography Tumor Registry at FHCRC. He will lead the scientific team evaluating the clinical utility of study results and the feasibility of integrating a marker panel routinely into clinical care. He will work with the team to develop standards to evaluate markers. Dr. Ramsey will participate in the development of data collection instruments, to ensure that adequate data are collected for future cost-effectiveness analyses that would be conducted as part of translating study results into clinical practice. In addition, he will assist with general analysis and participate in manuscript and report preparation. Because Dr. Ramsey is a recipient of a National Cancer Institute career development award he will donate his salary until February 1, 2003.

Meg Mandelson, PhD, Epidemiologist, (5% FTE) Dr. Mandelson has investigated the characteristics, including breast density, of breast cancers that are not detected by mammography, and will collaborate with Dr. McIntosh in investigating candidate biomarkers that may complement mammography and improve screening performance. She will collaborate with Drs. Anderson and Clarfeld to develop risk assessment and sampling measures that incorporate breast density, mammography outcome, pedigree and other risk factor data, and participate in the development of study questionnaires and other data collection instruments.

Larry Kessler, ScD, Visiting Scientist, (5% FTE Months 1-6 of Year 01) Dr. Kessler is a visiting scientist from the Food and Drug Administration (FDA) where he holds the position of Director of the Office of Surveillance and Biometrics. Dr. Kessler's background includes over ten years work in cancer control and surveillance at NCI and over five years experience at the FDA in medical device surveillance. He will bring a unique perspective to the project. Dr. Kessler will work closely with Drs. Ramsey and Drucker, as well as all investigators performing assays on sample sets, to explore the research and scientific issues involved in the development of a panel of markers that can be used clinically. Several aspects of translating the use of biomarkers from a laboratory to a clinical setting have not been well developed. Dr. Kessler will provide insight to bridge the gaps between the research community and the needs for marker panels to be brought through the regulatory mechanisms at the FDA. In addition to his consultation on methods and design, he will participate in manuscript writing.

Allen Gown, MD, Breast Pathologist (5% FTE) Dr. Gown is an internationally recognized expert in breast pathology and in the diagnostic and research applications of immunohistochemistry. He will provide expertise in expression at the tissue level of

angiogenesis and other markers. He will work closely with Drs. Yaziji, Rivkin and Schummer to identify breast cancer subtypes and "bad actors". He will interpret results from IHC studies of biomarkers on breast tissue samples and provide input on which biomarkers might have utility as diagnostic and prognostic indicators.

Hadi Yaziji, MD, Breast Pathologist (5% FTE) Dr. Yaziji is a breast pathologist with extensive experience in immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH). He will be responsible for activities in the PhenoPath laboratory. Dr. Yaziji will evaluate breast biopsies from study participants and work with Dr. Gown to interpret results from IHC studies of biomarkers on breast tissue samples. He will work closely with Drs. Gown, Rivkin and Schummer to identify breast cancer subtypes and "bad actors". Dr. Yaziji will evaluate tissue donated by participants for histologic prognosticators, as well as selecting foci of interest on the tissue sections for potential ancillary studies. He will work with Dr. Gown to interpret results from IHC studies of biomarkers on breast tissue samples and provide input on which biomarkers might have utility as prognostic indicators.

Brad Nelson, PhD, Immunologist (Contributed Consultant). Dr. Nelson has identified a panel of 12 tumor antigens that together are recognized by serum antibodies from 18/30 ovarian cancer patients compared to 0/20 normal controls. Preliminary results using a small number of early-stage breast cancer sera (n=12) indicate that several of these antigens are also immunogenic in breast cancer. Dr. Nelson is currently developing assays for these markers. Dr. Nelson will collaborate with Dr. Mann to explore markers that continue to look promising for potential inclusion in the biomarker panel.

Michel Schummer, PhD, Molecular Biotechnologist (Consultant 20% FTE Years 01-02; 20% FTE Years 03-04) Dr. Schummer is a Senior Research Scientist at the Institute for Systems Biology, and has experience conducting laboratory procedures to measure gene expression. Dr. Schummer will collaborate with Dr. Kiviat to ensure integration of the newest molecular approaches to genomics and proteomics in the laboratory work. Dr. Schummer will maintain ongoing communication with Dr. Kiviat regarding additional PCR markers that become available over the period of the grant, so that they can be incorporated into this study. He and will work closely with Drs. Kiviat and Karlan on methods for extraction, amplification and preservation of mRNA from tissue for molecular profiling work in Years 1-2 and will be responsible for molecular profiling of breast cancer tissues in Years 3-4. Dr. Schummer will also collaborate with Drs. Hellstrom, Mills and Kiviat to investigate gene expression in breast tissues. He will work closely with Drs. Gown, Yaziji and Rivkin to identify breast cancer subtypes and "bad actors". Dr. Schummer will help ensure that the protocols for processing and handling of macrodissected tissues will preserve the integrity of the molecules that will later be extracted from tissue specimens, including RNA, DNA and protein.

Ingegerd Hellstrom, PhD, Immunologist (5% FTE) Dr. Hellstrom is an expert in the development of antibody-based tests to detect shed and secreted proteins expressed by tumor, and organ-specific antigens that are amplified by tumor growth. She will work closely Drs. Mills and Kiviat to develop assays for genes identified in breast cancer pathways. Dr. Hellstrom will test an assay to measure mesothelin using the Assay Refinement/Triage set of specimens. If it appears useful for the panel, she will then measure mesothelin and other proteins that meet the criteria for initially promising results in the Panel Definition Set. She will collaborate with Dr. Mills to develop ELISA assays necessary to facilitate his work in lipid markers, and with Dr. Kiviat on an antibody for mammaglobin.

Gordon Mills, MD, PhD, Molecular Oncologist (5%) Dr. Mills will be responsible for laboratory science conducted at MD Anderson Cancer Center. His overall responsibility will be to study lipid markers that may complement mammography. He will use serum samples from the

Assay Refinement/Triage Set to refine the assay to measure LPA and other lipid markers. In addition, he will measure the lipid markers in the panel development set of serum samples. Dr. Mills will provide leadership and guidance for the development of detailed specimen processing protocols to ensure consistent measurement of lipid markers in serum samples. He will also collaborate with Drs. Schummer, Hellstrom, and Kiviat to investigate gene expression in breast tissues.

Gary Mann, MD, Immunologist (5% FTE) Dr. Mann will be responsible for activities in the Tumor Immunology Laboratory at the UW. He will use serum samples from the Assay Refinement/Triage Set and Panel Development Set to refine the assays to measure for antibodies to HER2, p53, and IGFBP-2. He will participate in the evaluation of laboratory results and the development and validation of the marker panel.

Irena King, PhD, Lab Director (5% FTE) Dr. King will be responsible for activities in the PHS Core Lab. She will measure VEGF and HGF in both the Assay Refinement/Triage Set and Panel Development set of plasma samples. In addition, Dr. King will oversee all scientific and quality control activities of the project as they relate to blood processing, storage and analysis. Dr. King will supervise Kathy O'Briant, the Research Technician who will provide assistance in all of the study laboratories in Years 1-3, and who will conduct the assays for the Validation Panel Set in Dr. King's laboratory in Years 3 and 4. Dr. King will be responsible for ensuring identical processing and storage of all specimens as well as coordinating the completion of serum-assays performed in off-site laboratories. Dr. King will also manage and coordinate the transfer of serum specimens between study sites when necessary. She will work with Dr. Urban and Ms. O'Briant to develop a protocol for the transfer and tracking of specimens from designated study freezers to other laboratories for their initial and on-going assay analysis. She will also lend her expertise to the evaluation of serum assays and will participate in manuscript preparation.

Clinicians

Scott Karlan, MD, Cedars-Sinai Breast Surgeon (Consultant 20% FTE) Dr. Karlan is a leading breast surgeon who has participated in research activities at Cedars-Sinai involving tissue collection and biomarker development. Dr. Karlan will oversee recruitment, enrollment and specimen collection from women undergoing biopsy for suspected breast cancer at Cedars Sinai Medical Center. He will travel to Seattle once in each year for an All-Investigator Meeting and will participate in additional All-Investigator meetings via conference call or web interface. See Cedars-Sinai subcontract.

Beth Karlan, MD, Gynecologic Oncologist (5%FTE; 1% compensated, 4% donated) Dr. Karlan has extensive experience in cancer screening and has collaborated with Dr. McIntosh in the past on the evaluation of markers for ovarian cancer screening. She will participate in the evaluation of laboratory results and the development and validation of the marker panel. Dr. Karlan will work closely with Drs. Schummer and Kiviat on methods for extraction, amplification and preservation of mRNA from tissue for molecular profiling work. Dr. Karlan will participate in conference calls and be available via email to collaborate with investigators in Seattle. She will travel to Seattle annually to participate in an All-Investigator Meeting and will participate in additional Investigator meetings via conference call or web interface. She will participate in manuscript and report preparation. See Cedars-Sinai subcontract.

Mariann Drucker, MD, Swedish Medical Center Radiologist (5% FTE). Dr. Drucker is a highly experienced mammographer in the Swedish Breast Care Center. She will provide clinical guidance and expertise to the project about breast cancer screening and will help interpret mammography data. She has been an investigator on the Mammography Tumor Registry (MTR) since 1994 and has served as the liaison to the medical community in Washington State and as the primary contact for radiologists participating in the MTR project. She will supervise

interactions between project staff and radiologists and their staff. Dr. Drucker, her associates and their staff, will administer the consent to contact form and Screening Questionnaire to patients and will invite women undergoing stereotactic biopsies to participate. She will work with Drs. Ramsey and Kessler and Ms. McAree to address the clinical utility of the panel of biomarkers. She will attend Investigator and Interdisciplinary Working Group meetings and provide leadership in interpreting the clinical relevance of mammography findings.

Saul Rivkin, MD, Oncologist (3% FTE) Dr. Rivkin is a well-known breast cancer oncologist in the Seattle community, practicing at Swedish Medical Center. Dr. Rivkin will serve as a liaison between study investigators and the clinical community, especially clinicians providing breast cancer care. In this role, Dr. Rivkin will facilitate and encourage participation by clinicians in the Interdisciplinary Working Group for which he will serve as Co-Chair. Dr. Rivkin has a similar role for an ovarian cancer research program in Seattle, and has been successful in bringing the clinical perspective to scientific studies. He will work closely with Drs. Gown, Yaziji, and Schummer to identify breast cancer subtypes and "bad actors". Dr. Rivkin will also provide scientific leadership for the evaluation of VEGF as a candidate for inclusion in the biomarker panel.

Richard Clarfeld, MD, Swedish Medical Center Breast Surgeon (Contributed Consultant) Dr. Clarfeld is a leading Seattle breast surgeon who has been an investigator on other FHCRC breast studies involving tissue collection. He will notify the study of patients scheduled for breast biopsy or surgery so the SCS can obtain informed consent pre-operatively, draw blood and attend surgeries to collect tissue on patients with large tumors that could potentially yield tissue for study purposes. He will collaborate with Drs. Anderson and Mandelson to develop risk assessment and sampling measures that incorporate breast density, mammography outcome, pedigree and other risk factor data, and participate in the development of study questionnaires and other data collection instruments. He will be a member of the Interdisciplinary Working Group.

Marc Horton, MD, Swedish Medical Center Breast Surgeon (Contributed Consultant) Dr. Horton is an experienced breast surgeon. His surgical practice is located on the same floor as the blood collection clinic for the Marsha Rivkin Ovarian Cancer Research Center, which can be used for this Center's blood draws. Dr. Horton and his partners will notify the study of patients scheduled for breast biopsy or surgery so a SCS can obtain informed consent pre-operatively, draw blood and attend surgeries to collect tissue on patients with large tumors that could potentially yield tissue for study purposes. He will be a member of the Interdisciplinary Working Group.

David Needle, MD, Swedish Medical Center Breast Surgeon (Contributed Consultant) Dr. Needle is an experienced breast surgeon and member of a large surgical practice. Surgery office staff will work closely with the SCS and will notify the study of patients scheduled for breast biopsy or surgery so the SCS can obtain informed consent pre-operatively, draw blood and attend surgeries to collect tissue on patients in their practice with large tumors that could potentially yield tissue for study purposes.

David Dwyer, MD, Swedish Medical Center Radiologist (Contributed Consultant). Dr. Dwyer is the Director of Radiology for the Swedish Breast Care Center and oversees the activities of this facility. Dr. Dwyer, his associates and staff, will administer the consent to contact form and Screening Questionnaire to patients and will invite women undergoing stereotactic biopsies to participate. He will attend Investigator and Interdisciplinary Working Group meetings and assist in interpreting the clinical relevance of mammography findings.

Janice Stracener, MD, Swedish Medical Center Radiologist (Contributed Consultant). Dr. Stracener is a highly experienced mammographer in the Swedish Breast Care Center and is

currently the SBC liaison to the Mammography Tumor Registry, participating in the Radiologist Advisory Committee. Dr. Stracener, her associates and their staff, will administer the consent to contact form and Screening Questionnaire to patients and will invite women undergoing stereotactic biopsies to participate. She will attend Investigator and Interdisciplinary Working Group meetings and assist in interpreting the clinical relevance of mammography findings.

Patient Registry and Specimen Repository Staff

Shirley Gough, RN, Research Nurse, (50% FTE) Ms. Gough has extensive experience in the breast cancer care clinical setting, and will manage the Patient Registry, responsible for all activities that involve contact with women or their physicians or the data that describes them, including patient contact, data collection activities and the patient tracking system. She will be responsible for implementing the components of this study involving physician and participant interaction, including participant recruitment, retention, and compliance. Ms. Gough will facilitate relationships with the breast cancer surgeons at SMC whose patients will be approached, and work with these physicians to develop efficient enrollment procedures to minimize impact on patient flow in the clinics. She will work with the Breast Care Center to coordinate enrollment of women undergoing mammograms and biopsies. She will work closely with Ms. McAree and Drs. Ramsey, Kessler and Drucker to address the clinical utility of the panel of biomarkers. She will oversee and monitor the recruitment process, and work with Ms. Shaw to develop standardized recruitment and compliance reports accessible to all investigators via the Flex KB collaborative site. Ms. Gough will attend biopsy appointments of women who have provided permission, conduct informed consent, and perform blood draw. Ms. Gough will oversee weekly transfer of serum specimens from Dynacare laboratories to study freezers. She will conduct quality assurance checks on specimen collection forms, pathology data forms, and freezer inventory. Ms. Gough will also review the pathology reports for patients who develop cancer to collect information on estrogen and progesterone receptor assays, HER2, p53 and other markers. She will review the reports of in situ cancers to ascertain the histologic subtypes of DCIS because CSS and WSCR coding guidelines for histology lead to a broad grouping of DCIS and lose some of the more specific information on subtypes which are of interest to investigators. Ms. Gough will supervise the Specimen Collection Specialists and Alisa Larson, Program Assistant.

Kathy O'Briant, Research Technician (100% FTE) Ms. O'Briant is very experienced in all of the laboratory procedures required for the proposed work. She will manage the Specimen Repository, including all activities surrounding specimens from the time of collection to analysis and will be the contact person for all requests and communication. Under the direction of Dr. Kiviat, she will be responsible for specimen inventory control, the specimen tracking system and the Specimen Review Committee. To promote good communication between laboratories, Kathy O'Briant will serve as liaison between the laboratory scientists and statisticians and will supervise the TBN Research Technician who will work in the various laboratories. She will provide assistance with assay development, refinement, and validation in all of the collaborating laboratories. She will compile complete documentation of laboratory procedures and protocols. She will work with Dr. Kiviat to develop lab procedures to extract RNA from small amounts of breast tissue. She will work closely with the laboratory scientists on the development of assays for genes identified in breast cancer pathways and the identification of breast cancer subtypes and "bad actors". Ms. O'Briant will conduct the assays on the Panel Validation Set in Dr. King's laboratory (Years 3 and 4). She will work closely with Ms. Gough to develop and monitor collection procedures. She will also work closely with the Informatics staff on the redesign and maintenance of the specimen tracking system (STS) and the implementation of the FlexKB to ensure both systems meet the needs of the laboratory scientists. Ms. O'Briant will supervise the Research Technician hired in Year 03.

TBN, Research Technician (100% FTE in Years 03 and 04) The Laboratory Research Technician will provide assistance in all of the study laboratories and, along with Ms. O'Briant, will conduct assays on the Panel Validation Set in Dr. King's laboratory. S/he will also be responsible for facilitating communication among laboratories and documenting lab procedures. All activities will be coordinated by Ms. O'Briant.

Kaysey Orlowski, Specimen Collection Specialist (50% FTE Year 01, 100% FTE Year 02-04) Ms. Orlowski is a trained phlebotomist and experienced Specimen Collection Specialist, currently performing these duties for the Ovarian SPORE. She will be assigned to Dr. Clarfeld's surgical practice and be responsible for conducting informed consent for donation of blood and tissue specimens for patients enrolled at that practice. To facilitate this process, work space for the SCS will be provided in Dr. Clarfeld's practice. Ms. Orlowski will perform blood draw on consenting patients for whom tissue will not be collected. She will monitor the surgical schedule, and attend surgeries of enrolled women when the surgeon has indicated that excess tissue may be available. In these cases, she will collect blood and tissue in the operating room. Although her principal assignment is in Dr. Clarfeld's practice, his office is within walking distance of the offices of Dr. Horton and the SBC and she will be available for collections at other locations. When time allows, Ms. Orlowski will assist with the substantial data entry volume that will be required to enter the 1-page screening questionnaire completed by women undergoing mammograms at the Breast Care Center. Ms. Orlowski will also assist with data entry of the epidemiologic Baseline Questionnaires, and the annual health status forms from women donating specimens. For each specimen collection, Ms. Orlowski will complete a detailed specimen collection form which indicates the specimen type and tracking number, data and time of collection, patient UPN, and associated data. She will use this form to enter collected specimens into the computerized inventory system.

Josh Sallin, Specimen Collection Specialist (50%FTE Year 01, 100% FTE Years 02-04) Mr. Sallin is a trained phlebotomist and experienced Specimen Collection Specialist, currently performing these duties for the Ovarian SPORE. He will be assigned to Dr. Needle's surgical practice and be responsible for conducting informed consent for donation of blood and tissue specimens for patients enrolled at that practice. To facilitate this process, work space for the SCS will be provided in Dr. Needle's practice. Mr. Sallin will perform blood draw on consenting patients for whom tissue will not be collected. He will monitor the surgical schedule, and attend surgeries of enrolled women when the surgeon has indicated that excess tissue may be available. In these cases, he will collect blood and tissue in the operating room. Although his principal assignment is at the PacMed Clinic, the clinic is located within .3 miles of SMC and the offices of Dr. Clarfeld, Dr. Horton and the SBC and Mr. Sallin will be available for collections at other locations. When time allows, Mr. Sallin will assist with the substantial data entry volume that will be required to enter the 1-page screening questionnaire completed by women undergoing mammograms at the Breast Care Center. Mr. Sallin will also assist with data entry of the epidemiologic Baseline Questionnaires, and the annual health status forms from women donating specimens. For each specimen collection, Mr. Sallin will complete a detailed specimen collection form which indicates the specimen type and tracking number, data and time of collection, patient UPN, and associated data. He will use this form to enter collected specimens into the computerized inventory system.

Rachel Song, Program Assistant (50% FTE Year 01; 75% FTE Years 02-04) Ms. Larson is an experienced interviewer who is responsible for recruitment interviewing and intervention support for two ongoing studies. Ms. Larson will provide support to all recruitment and intervention activities, including assembly and distribution of recruitment and enrollment materials, data entry of participant questionnaires, assembly and distribution of blood collection kits, assisting with specimen transfers and freezer inventory, conducting follow-up and reminder calls for all

participants who are overdue for annual blood collections. 8,600 women will be asked to complete the Consent to Contact and 1-page screening questionnaire each year, and Ms. Larson will be responsible for data entry of those questionnaires from women who return them. She will be responsible for preparing enrollment/blood collection packets for 675 participants in year 1, and 400 participants in each subsequent year. She will conduct follow-up calls with participants who fail to complete their blood draws within the expected time frame. Ms. Larson will provide overall support to the staff leadership, coordinating special projects as needed. In particular, she will be available to assist Ms. Gough with special projects related to recruitment, and to assist Ms. O'Briant with Specimen Repository management tasks.

Informatics Staff

Steve Zeliadt, Informatics Manager, (50% FTE) Mr. Zeliadt has extensive experience in database development. He manages the Mammography Tumor Registry (MTR). Mr. Zeliadt will be responsible for managing informatics including the Specimen Tracking System (STS), access to and analysis of data, report generation and web-based communication tools (FlexKB). The broad scope of his responsibility will include database design and development, maintenance and updates of the linked mammography tumor registry, design and development of data collection instruments, coordinating investigator requests for analysis datasets, development of standardized reports describing the Specimen Repository, and management of the STS. Mr. Zeliadt will coordinate quarterly data transfers from radiology facilities to the study office and identification of high risk patients based on mammography and questionnaire data, and linkage of mammography data to the SEER/WSCR registries to identify cancers in the screening population. Mr. Zeliadt will develop task lists and timelines for the database development work, and work with Carole Shaw, the Database Manager, and programmers to ensure that study requirements for informatics support are met. Mr. Zeliadt will serve as liaison with Lauren Clarke, the consultant developing the FlexKB system to support real time inter-institutional communication and project updates between investigators. He will work with Ms. O'Briant to support the Specimen Review Committee, and will be responsible for compiling detailed specimen inventory information for the committee's reference in making specimen allocation decisions. Mr. Zeliadt will work with Carole Shaw to identify specimens to be transferred to project investigators, and will ensure that all appropriate scientific approvals are in place. Mr. Zeliadt will supervise the Database Manager and Informatics Specialist.

Sue Peacock, MS, Statistical Research Associate (50% FTE) Ms. Peacock is a Masters level epidemiologist with experience managing and analyzing large datasets. Ms. Peacock will be responsible for statistical procedures including data quality control, dataset cleaning and analysis for all study data. She will work closely with Drs. McIntosh and Anderson to evaluate the results of surveys and questionnaires, and will provide statistical analysis support to study investigators.

Carole Shaw, Database Manager (50% FTE) Ms. Shaw currently has responsibility for two databases which will be used for the study: the linked mammography tumor registry, and the STS which is used to track inventory and laboratory results for biological specimens for the ovarian SPORE. Ms. Shaw will continue to manage and oversee all database activities. She will develop a study database to identify all subjects who have agreed to participate and routines to select and identify eligible participants. Other features of the database will include reports documenting the status of participants and generation of follow-up letters for serial blood draws. She will analyze the current specimen tracking system and develop revised software design specifications necessary for this study and a plan for porting existing data in the legacy system to the new data structure. She will be responsible for ongoing database design and management, including data collection, data validation, and quality assurance checks on the linkage process as the database becomes more complex. She will be responsible for resolving disparity among linked data items, and for ensuring confidentiality. Ms. Shaw will make any adaptations to the STS to ensure that it

meets the needs of this study, and for development of reports documenting the status of specimens collected for the study, including inventory, tracking, and laboratory value reporting. Ms. Shaw will supervise the Programmer, Shelly Hager, and Data Coordinator, Caroline Smith, and will be the primary contact for data management personnel for the exchange of data between participating laboratories and mammography facilities.

Appendix C
Logistics of Specimen Collection

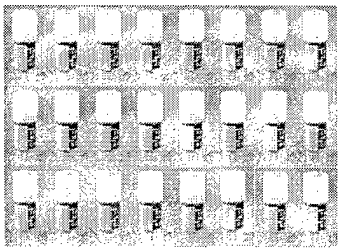
Proposed Blood Collection and Distribution for Breast Study

40c  Plain non-barrier

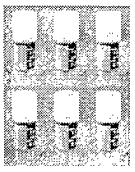
Blood Draw

 10c Potassium-EDTA

Product



1 ml aliquots of serum



1 ml aliquots of plasma

Distribution

→ **Cedar-Sinai Medical Center**
-DNA and RNA extraction

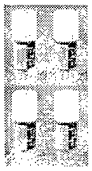
→ **Fred Hutchinson Cancer Research Center**
-Cathepsin, Cyclin-D1, Topoisomerase IIA

→ **MD Anderson**
-Lipid Markers
(LPA, LPC, LPI, LPS, MAG, SPC, S1P)

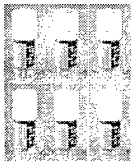
→ **Pacific Northwest Research Institute**
-Development of antibodies, sandwich ELISAs

→ **Phenopath Laboratories**
-VEGF, HGF

→ **Swedish Medical Center**
-VEGF



→ **University of Washington**
-Mammoglobin, Her2/neu, IGFBP-2



→ **FHCRC Repository**

→ **Cedar-Sinai Medical Center**
-DNA and RNA extraction

→ **Fred Hutchinson Cancer Research Center**
-Cathepsin, Cyclin-D1, Topoisomerase

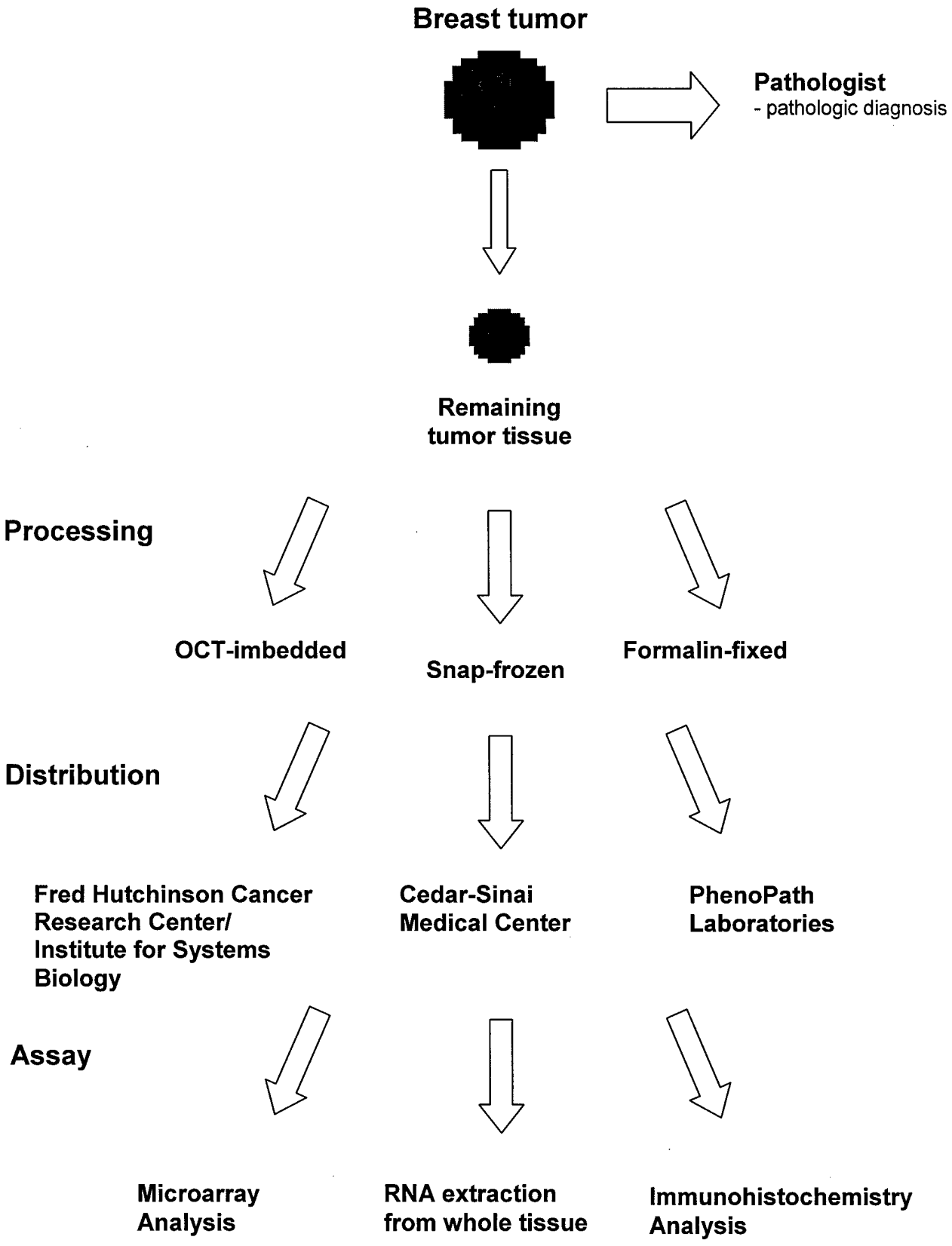
→ **MD Anderson**
-Lipid Markers
(LPA, LPC, LPI, LPS, MAG, SPC, S1P)

→ **Pacific Northwest Research Institu**
-Development of antibodies, sandwich ELIS

→ **Phenopath Laboratories**
-VEGF, HGF

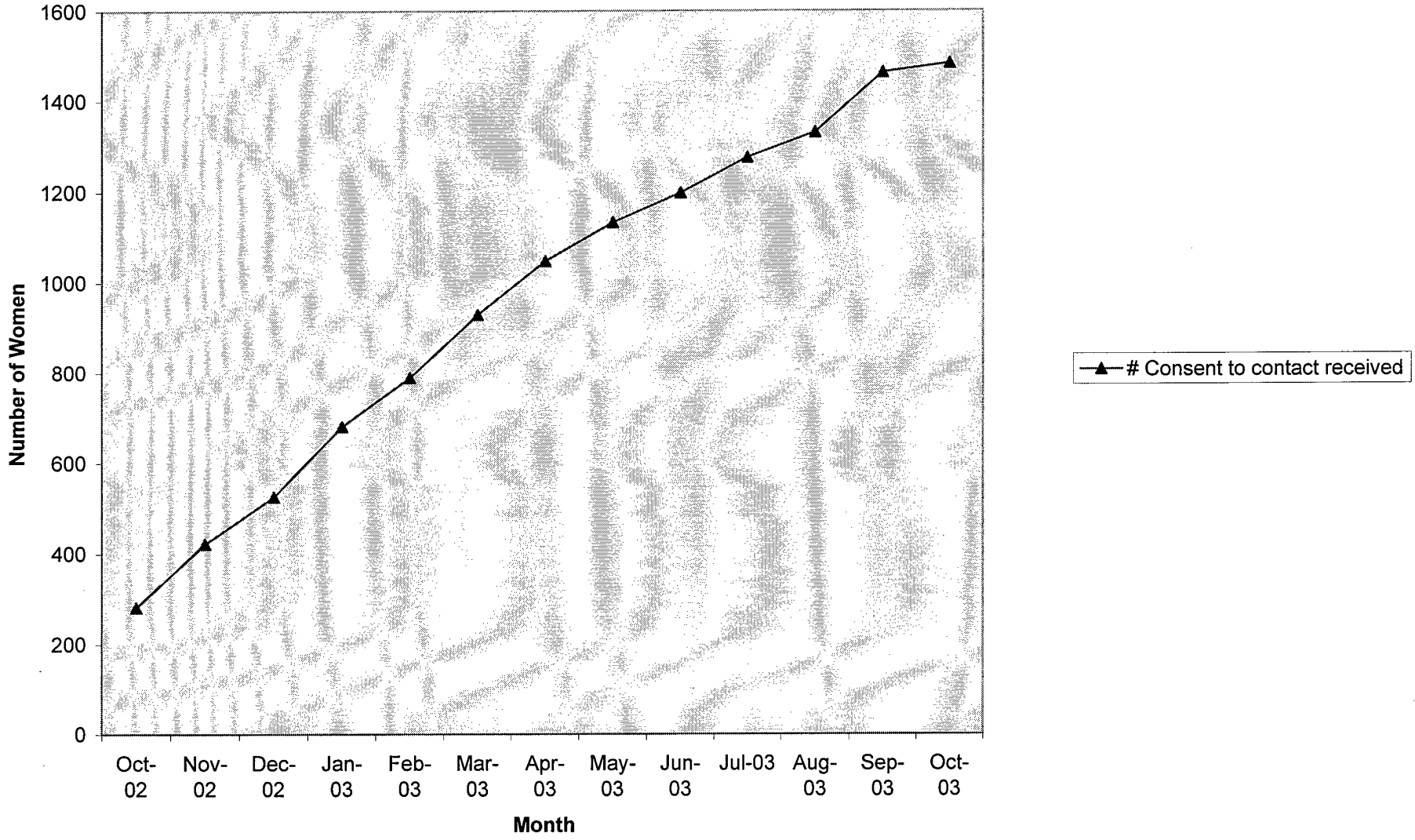
→ **University of Washington**
-Mammoglobin, Her2/neu, IGFBP-2

Proposed Tissue Collection and Distribution for Breast Study



Appendix D
Enrollment into the Registry

Cumulative Consent to Contact Collection at SBCC



Appendix E
Data Collection Instruments

Instruments:

1. One-page Screening Questionnaire
2. Epidemiologic Risk Factor Questionnaire- Baseline Questionnaire
3. Health Status Form
4. Patient Clinical Status at Enrollment
5. Clinical Status Follow Up
6. Participant Pathology at Diagnosis

Instrument 1

One-page Screening Questionnaire

Fred Hutchinson Cancer Research Center

Packet I.D. # «Packetid»

Cancer Research Registry Questionnaire

A. What is today's date?

___ ___ / ___ ___ / ___ ___ ___ ___
month day year

B. What is your date of birth?

___ ___ / ___ ___ / ___ ___ ___ ___
month day year

C. What is your social security number? *(Used for data tracking purposes only)*

___ ___ ___ / ___ ___ / ___ ___ ___ ___

D. What is your racial background? *(Check all that apply)*

- ☐ 5 White/Caucasian
- ☐ 3 Black or African American
- ☐ 1 American Indian/Alaska native
- ☐ 6 Asian
- ☐ 7 Native Hawaiian or other Pacific Islander
- ☐ 8 Other

E. What is your ethnic background? *(Check all that apply)*

- ☐ 1 Hispanic or Latino
- ☐ 2 Ashkenazi Jewish
- ☐ 9 Other *(Specify)* _____

PERSONAL HISTORY

1. Have you ever had breast cancer?

- ☐ 0 No
- ☐ 1 Yes → **If yes, in which breast?**
  - ☐ 1 Left
  - ☐ 2 Right
  - ☐ 3 Both

If yes, what was your age when you were diagnosed?

_____

2. Have you ever had ovarian cancer?

- ☐ 0 No
- ☐ 1 Yes → **If yes, what was your age when you were diagnosed?**

_____

3. Have your menstrual periods stopped permanently? *(Check best answer)*

- ☐ 0 No
- ☐ 1 No, but my periods are less frequent
- ☐ 2 I now have bleeding from hormone replacement therapy
- ☐ 3 Yes, my periods stopped naturally (menopause)
- ☐ 4 Yes, my periods stopped due to surgery
- ☐ 9 Not sure

If yes, how old were you when your periods stopped?

_____

FAMILY HISTORY OF BREAST AND OVARIAN CANCER

Questions 4 and 5 ask about your FEMALE BLOOD relatives

4. Mother and Grandparents	Please check if she ever had breast cancer	Please check if she was under age 50 when diagnosed with breast cancer	Please check if she ever had ovarian cancer
Mother	☐	☐	☐
Father's mother (paternal grandmother)	☐	☐	☐
Mother's mother (maternal grandmother)	☐	☐	☐

5. Sisters, Aunts and Nieces	How many have had breast cancer?	How many were under 50 when diagnosed with breast cancer?	How many have had ovarian cancer?
Your sisters	_____	_____	_____
Your daughters	_____	_____	_____
Father's sisters (paternal aunts)	_____	_____	_____
Mother's sisters (maternal aunts)	_____	_____	_____
Your sibling's daughters (nieces)	_____	_____	_____

6. Though rare, sometimes men are diagnosed with breast cancer. Have any of your MALE BLOOD relatives had breast cancer?

- ☐ 0 No
- ☐ 1 Yes → **If yes, who was the relative?**
  - ☐ 1 Your father, son, or brother
  - ☐ 2 Father's father or father's brother (your paternal grandfather or uncle)
  - ☐ 3 Mother's father or mother's brother (your maternal grandfather or uncle)
  - ☐ 4 Sibling's son (your nephew)
  - ☐ 5 Other male relative

PLEASE READ AND SIGN

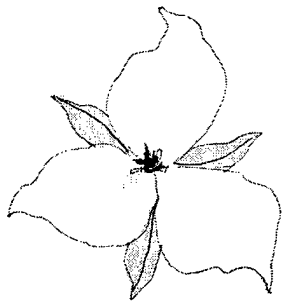
This questionnaire contains information that researchers can use to select participants who fit the criteria for their specific studies. By completing this form you give permission for the information you provide to be maintained indefinitely in a confidential database as a potential participant in future cancer research studies. There is no anticipated risk in providing information on your family and medical history. The database is strictly confidential and highly secure.

X _____
Signature

Thank you for completing this form. Volunteer participants are very important to the success of research.
If you have any questions, please contact Kate Watabayashi, at 1-800-732-4589, or (206) 667-5624.

Instrument 2

Epidemiologic Risk Factor Questionnaire
Baseline Questionnaire



Breast Cancer Early Discovery Study

Baseline Questionnaire

How to Fill Out this Questionnaire

This questionnaire asks you a variety of questions about your general health, medical history, lifestyle, opinions about cancer screening, and family history of cancer. It takes about 30 minutes to complete. All of your answers will be kept strictly confidential.

Before you begin, please note the following:

1. If a question asks you to "check one" answer, please check the one that best describes you.
2. If you are unsure about how to answer a question, make your best guess. If you cannot provide a guess or estimate, please check or write "Don't know."
3. Providing answers is completely voluntary and you may choose to leave some items blank.
4. Some questions ask about brothers and sisters. If you have half-brothers or half-sisters (siblings that have only one of the same parents as you), please report their health history under the categories marked for full brothers and full sisters.
5. Questions about primary cancer refer to the place in the body where the cancer started, not where the cancer spread.

Please return your completed questionnaire to the study office in the provided self-addressed stamped envelope. Thank you for taking the time to complete this questionnaire. Your participation is greatly appreciated!

Fred Hutchinson Cancer Research Center
Attn: Breast Cancer Early Discovery Study (PI: Nicole Urban, ScD); P.O. Box 19024 (MP-900);
Seattle, Washington 98109
(206) 667-5624

Section A

Our first section asks about your background and personal information.

1. What is today's date?

|__|__| month |__|__| day |__|__|__|__| year

1a. What is your telephone number?

|__|__|__| |__|__|__| |__|__|__|__|

☐$_1$ This is my home phone number
☐$_2$ This is my work number

2. What is your date of birth?

|__|__| month |__|__| day |__|__|__|__| year

3. What is the date of your last menstrual period? *(If less than 1 year ago)*

|__|__| month |__|__| day |__|__|__|__| year

4. What is your height?

|__| feet |__|__| inches

5. What is your weight?

|__|__|__| pounds

6. What is your ethnic background? *(Check all that apply)*

Self	Biologic mother	Biologic father		
☐	☐	☐	1	White/Caucasian
☐	☐	☐	2	Black or African American
☐	☐	☐	3	Native American/Aleutian/Eskimo
☐	☐	☐	4	Chinese
☐	☐	☐	5	Japanese
☐	☐	☐	6	Filipino
☐	☐	☐	7	Hawaiian

Continued on next page

Self	Biologic mother	Biologic father	
☐	☐	☐	8 Korean
☐	☐	☐	9 Asian Indian (Pakistani, Sri Lankan, Bhutanese, Bangladeshi
☐	☐	☐	10 Vietnamese
☐	☐	☐	11 Laotian
☐	☐	☐	12 Hmong
☐	☐	☐	13 Kampuchean (Cambodian)
☐	☐	☐	14 Thai
☐	☐	☐	20 Micronesia, NOS*
☐	☐	☐	21 Chamorro
☐	☐	☐	22 Guamanian, NOS*
☐	☐	☐	25 Polynesian, NOS*
☐	☐	☐	26 Tahitian
☐	☐	☐	27 Samoan
☐	☐	☐	28 Tongan
☐	☐	☐	30 Melanesian, NOS*
☐	☐	☐	31 Fiji Islander
☐	☐	☐	32 New Guinean
☐	☐	☐	96 Asian, other (including Burmese, Indonesian, Asian NOS*, and Oriental NOS*
☐	☐	☐	97 Pacific Islander, NOS*
☐	☐	☐	98 Other:
☐	☐	☐	99 Unknown

**NOS = Not Otherwise Specified*

Are you of Spanish or Hispanic origin or descent? *(Check all that apply)*
Note: Brazilian and Portuguese considered Non-Spanish, Non-Hispanic

Self	Biologic mother	Biologic father	
☐	☐	☐	0 Non-Spanish, Non-Hispanic*
☐	☐	☐	1 Mexican, including Chicano, Not Otherwise Specified
☐	☐	☐	2 Puerto Rican
☐	☐	☐	3 Cuban
☐	☐	☐	4 South or Central American (except Brazilian, see note below)
☐	☐	☐	5 Other specified Spanish origin (includes European)
☐	☐	☐	6 Spanish, Hispanic, or Latino, Not Otherwise Specified
☐	☐	☐	7 Spanish surname only
☐	☐	☐	9 Unknown

7. What is the highest level of schooling you have COMPLETED?

☐$_0$ 8 years or less
☐$_1$ Some high school
☐$_2$ High school grad/GED
☐$_3$ Some college or technical school
☐$_4$ Graduated college or beyond
☐$_9$ Unknown

8. Is your mother of Ashkenazi (Eastern European) Jewish descent?

☐$_0$ No
☐$_1$ Yes
☐$_9$ Unknown

9. Is your father of Ashkenazi (Eastern European) Jewish descent?

☐$_0$ No
☐$_1$ Yes
☐$_9$ Unknown

10. Are you adopted?

☐$_0$ No
☐$_1$ Yes
☐$_9$ Unknown

Section B

These next questions are about your reproductive history.

11. Have you ever had a menstrual period?

☐$_0$ No ⟶ ***If no, go to question 19***
☐$_1$ Yes
☐$_9$ Unknown

12. How old were you when you started having your menstrual periods?

|__|__| Years old

13. What is (was) the average number of days from the start of one period to the start of another? *(Length of menstrual cycle is usually between 25 – 35 days)*

|__|__| Days

14. When you were last menstruating, are (were) your menstrual cycle lengths generally predictable within 10 days?

☐$_0$ No
☐$_1$ Yes
☐$_9$ Unknown

15. When you were last menstruating, do (did) you experience discomfort during your menstrual period? *(Check only one)*

☐$_0$ No discomfort
☐$_1$ Mild cramps or infrequent discomfort, medication seldom needed
☐$_2$ Moderate cramps, medication usually needed
☐$_3$ Severe cramps, medication and bed rest needed

16. Have your regular periods stopped for 3 or more menstrual cycles **for any reason**? *(e.g. natural menopause, hysterectomy, the removal of both ovaries, radiation/chemotherapy treatment, other)*

☐$_0$ No
☐$_1$ Yes →
☐$_9$ Unknown

17. At what age did your periods last stop for 3 or more menstrual cycles?

|__|__| Years old

18. Which of the following best describes why your menstrual cycle stopped? *(Check only one)*

☐$_0$ Natural menopause (change of life)
☐$_1$ Surgery (either uterus and/or ovaries were surgically removed)
☐$_2$ Radiation
☐$_3$ Medication or drug therapy
☐$_4$ Other *(Specify)* _____

19. Have you ever had a hysterectomy for any reason?

☐$_0$ No
☐$_1$ Yes →
☐$_9$ Unknown

20. At what age did you have a hysterectomy?

|__|__| Years old

21. Have you ever had your left ovary removed for any reason?

☐$_0$ No
☐$_1$ Yes
☐$_9$ Unknown

22. At what age did you have your left ovary removed?

|__|__| Years old

23. Have you ever had your right ovary removed for any reason?

☐$_0$ No
☐$_1$ Yes
☐$_9$ Unknown

24. At what age did you have your right ovary removed?

|__|__| Years old

25. If your ovaries were removed, why was/were the ovary/ovaries removed? *(Check only one)*

☐$_1$ Pelvic infection
☐$_2$ Ovarian torsion (an ovary that twisted on itself)
☐$_3$ Endometriosis
☐$_4$ An ovarian cyst not due to endometriosis
☐$_5$ Ovarian cancer
☐$_6$ To prevent or reduce risk of ovarian or other cancer (prophylaxis)
☐$_7$ Other *(Specify)* _____

26. Have you ever used pills, OTHER THAN BIRTH CONTROL PILLS, that contain female hormones (such as estrogen and progesterone) for **any reason** (e.g. relief or prevention of menopausal symptoms, irregular periods, or prevention of diseases such as bone loss or heart disease)?

☐$_0$ No
☐$_1$ Yes
☐$_9$ Unknown

27. Please complete the table below indicating whether you have EVER TAKEN any of the hormonal supplements listed for **any reason** (e.g. to relieve menopausal symptoms or for prevention of menopausal symptoms.

Hormone supplement	Have you ever used?	Are you currently using?	Age first began using	Age last used	Total number of years on medication
27a. Estrogen or estradiol only (e.g. Premarin, Estrace, Estratab, Ortho-est, Ogen, Gynodiol, Cenestin, or Alora)	☐$_0$ No ☐$_1$ Yes ☐$_9$ Unknown	☐$_0$ No ☐$_1$ Yes	___	___	___
27b. Progestinor progesterone only (e.g. Provera, Amen Cycrin, Megace, Curratab, Prometrium, or Aygestin)	☐$_0$ No ☐$_1$ Yes ☐$_9$ Unknown	☐$_0$ No ☐$_1$ Yes	___	___	___
27c. Both estrogen and progesterone, 2 types of female hormones in the same pill (e.g. Prempro, Premphase)	☐$_0$ No ☐$_1$ Yes ☐$_9$ Unknown	☐$_0$ No ☐$_1$ Yes	___	___	___
27d. Patches containing female hormones (e.g. Estraderm, FemPatch, Alora, Climara Vivelle, or CombiPatch	☐$_0$ No ☐$_1$ Yes ☐$_9$ Unknown	☐$_0$ No ☐$_1$ Yes	___	___	___
27e. Natural hormone Therapy (e.g. phytoestrogens)	☐$_0$ No ☐$_1$ Yes ☐$_9$ Unknown	☐$_0$ No ☐$_1$ Yes	___	___	___

28. Have you ever used hormonal contraceptives in the form of birth control pills, implants, or injections for any reason other than menopause?

☐$_0$ No
☐$_1$ Yes →
☐$_9$ Unknown

29. How old were you when you first started taking hormonal contraceptives?

|_|_| Years old

30. How many months in total have you taken hormonal contraceptives?

|_|_|_| Months

31. Are you currently using hormonal contraceptives?

☐$_0$ No
☐$_1$ Yes
☐$_9$ Unknown

32. Are you currently pregnant or anticipating pregnancy in the next year?

☐$_0$ No
☐$_1$ Yes
☐$_9$ Unknown

33. How many pregnancies have you had which ended before you reached 6 months (miscarriages, ectopic pregnancies, etc.)?

|__|__|

34. How many pregnancies have you had which lasted beyond 6 months (all deliveries - both term and preterm)?

|__|__|

35. What was your age when you had your first live birth?

|__|__| Years old

36. What was your age when you had your last live birth?

|__|__| Years old

37. Have you had a tubal ligation (having your tubes tied)?

☐$_0$ No
☐$_1$ Yes ——→
☐$_9$ Unknown

38. What was your age when you had the tubal ligation?

|__|__| Years old

39. Did you ever try for one straight year or more to become pregnant and not become pregnant during that time?

☐$_0$ No ——→ ***If no, go to question 43***
☐$_1$ Yes
☐$_9$ Unknown

40. Did you or your partner ever visit a doctor, clinic, or hospital because of a difficulty of becoming pregnant?

☐$_0$ No
☐$_1$ Yes
☐$_9$ Unknown

41. If you had difficulty getting pregnant, which of these best describes the reason(s) you had difficulty getting pregnant? *(Check all that apply)*

☐$_1$ Problem with ovaries or hormones (including ovulation)
☐$_2$ Problem with fallopian tubes
☐$_3$ Problems with uterus or cervix (including endometriosis)
☐$_4$ Husband or male partner had a fertility problem
☐$_5$ Other fertility problems *(Specify)* _____
☐$_6$ No problem was ever found
☐$_9$ Unknown

42. Did you ever use a fertility drug for more than 1 year total in order to stimulate ovulation?

☐$_0$ No
☐$_1$ Yes
☐$_9$ Unknown

43. Have you ever taken any of the following fertility drugs? *(Check all that apply)*

☐$_0$ None
☐$_1$ Clomid
☐$_2$ Pergonal
☐$_3$ Lupron
☐$_4$ Other *(Specify)*_____
☐$_9$ Don't know

Section C

This section asks about cancer screening, your personal history of cancer and treatment.

44. Have you had a CA125 test? (commonly related to breast or ovarian cancer)?

☐₀ No
☐₁ Yes
→ Please enter the date(s) and the numerical results of those tests below. *(Best guess)*

Date of test (mm/dd/yyyy)	CA 125 value
___ ___/___ ___/___ ___ ___ ___	________
___ ___/___ ___/___ ___ ___ ___	________
___ ___/___ ___/___ ___ ___ ___	________
___ ___/___ ___/___ ___ ___ ___	________
___ ___/___ ___/___ ___ ___ ___	________
___ ___/___ ___/___ ___ ___ ___	________

45. Have you ever had a mammogram?

☐₀ No
☐₁ Yes
→ Please provide the date(s) and result(s) of your most recent mammogram(s). *(Best guess)*
*A **"Positive"** result indicates significant suspicion of malignancy to refer to biopsy.*
*An **"Equivocal"** result is an uncertain finding leading to a follow-up mammogram.*

Date of test (mm/dd/yyyy)	Result
___ ___/___ ___/___ ___ ___ ___	☐₀ Negative ☐₁ Positive ☐₃ Equivocal
___ ___/___ ___/___ ___ ___ ___	☐₀ Negative ☐₁ Positive ☐₃ Equivocal
___ ___/___ ___/___ ___ ___ ___	☐₀ Negative ☐₁ Positive ☐₃ Equivocal
___ ___/___ ___/___ ___ ___ ___	☐₀ Negative ☐₁ Positive ☐₃ Equivocal
___ ___/___ ___/___ ___ ___ ___	☐₀ Negative ☐₁ Positive ☐₃ Equivocal
___ ___/___ ___/___ ___ ___ ___	☐₀ Negative ☐₁ Positive ☐₃ Equivocal

46. Have you ever had an ovarian ultrasound?

☐$_0$ No
☐$_1$ Yes
→ Please provide the date(s) and result(s) of your ovarian ultrasound(s). *(Best guess)*

*A **"Positive"** result indicated a suspicion of malignancy (cancer).*
*An **"Equivocal"** result means that it is uncertain whether the finding is benign or malignant.*
*A **"Negative"** result means that the finding is most likely benign and the ovaries are normal.*
Transvaginal Sonography (TVS) is an ultrasound that is done inside the vagina.
A Transabdominal ultrasound is done externally over the lower part of the abdomen.

Date of ovarian ultrasound ***(mm/dd/yyyy)***	**TVS or transabdominal**	**Result**
__ __/__ __/__ __ __ __	________	☐$_0$ Negative ☐$_1$ Positive ☐$_3$ Equivocal
__ __/__ __/__ __ __ __	________	☐$_0$ Negative ☐$_1$ Positive ☐$_3$ Equivocal
__ __/__ __/__ __ __ __	________	☐$_0$ Negative ☐$_1$ Positive ☐$_3$ Equivocal
__ __/__ __/__ __ __ __	________	☐$_0$ Negative ☐$_1$ Positive ☐$_3$ Equivocal
__ __/__ __/__ __ __ __	________	☐$_0$ Negative ☐$_1$ Positive ☐$_3$ Equivocal
__ __/__ __/__ __ __ __	________	☐$_0$ Negative ☐$_1$ Positive ☐$_3$ Equivocal
__ __/__ __/__ __ __ __	________	☐$_0$ Negative ☐$_1$ Positive ☐$_3$ Equivocal
__ __/__ __/__ __ __ __	________	☐$_0$ Negative ☐$_1$ Positive ☐$_3$ Equivocal
__ __/__ __/__ __ __ __	________	☐$_0$ Negative ☐$_1$ Positive ☐$_3$ Equivocal

The following questions, 47-56, ask about genetic testing and are optional. You may choose to skip some or all of them.

47. Have you ever had genetic testing to evaluate your familial risk for cancer?

☐0 No → ***Go to question 57***
☐1 Yes
☐9 Unknown

48. Was a mutation (genetic change) found by the test?

☐0 No → ***Go to question 52***
☐1 Yes
☐9 Unknown

49. If a mutation was found, was it a

☐0 Disease-related mutation
☐1 Mutation of uncertain significance
☐9 Unknown

50. If a mutation was found, was it a mutation in the BRCA1 or BRCA2 gene?

☐0 No
☐1 Yes
☐9 Unknown

51. If a BRCA1 or BRCA2 mutation was found, was it a

☐1 BRCA1 mutation
☐2 BRCA2 mutation
☐3 Both
☐9 Unknown

52. Does a first-degree blood relative have a BRCA1 or BRCA2 mutation? *(Check only one)*
A first-degree blood relative is one of the following: mother, father, sister, brother, daughter, son.

☐0 No
☐1 Yes, disease-related mutation
☐2 Yes, mutation of uncertain significance
☐9 Unknown

53. Does a second-degree blood relative have a BRCA1 or BRCA2 mutation?
(Check only one)
A second-degree blood relative is one of the following: mother or father's sister, mother or father's brother, niece, nephew, grandmother, grandfather, granddaughter, grandson

☐$_0$ No
☐$_1$ Yes, disease-related mutation
☐$_2$ Yes, mutation of uncertain significance
☐$_9$ Unknown

54. Did the test result show a mutation in another (not BRCA1 or BRCA2) gene?

☐$_0$ No
☐$_1$ Yes →
☐$_9$ Unknown

55. In which of the following genes was the mutation?
(Check only one)

☐$_1$ HNPCC
☐$_2$ PTEN
☐$_3$ p53
☐$_4$ Other *(Specify)* _____
☐$_9$ Unknown

56. What was the result of your genetic test (from question 47)? *(Check only one)*

☐$_1$ Negative
☐$_2$ Positive (the testing confirmed mutation is present)
☐$_3$ Positive mutation and variant of unknown significance (VUS)
☐$_4$ Two or more VUS
☐$_5$ Testing was inconclusive
☐$_6$ Test results pending
☐$_9$ Unknown

57. Have you ever been diagnosed with cancer of any kind? (If no, skip to question #68)

☐$_0$ No
☐$_1$ Yes
☐$_9$ Unknown

58. What type of cancer and in which year was it diagnosed?
(List only primary cancers, that is the place in the body where the cancer started, not where it spread)

Primary cancer	Year of diagnosis
☐$_1$ Bladder	____
☐$_2$ Bone	____
☐$_3$ Brain	____
☐$_4$ Breast	____
☐$_5$ Cervix	____
☐$_6$ Colon	____
☐$_7$ Esophagus	____
☐$_8$ Head and neck	____
☐$_9$ Hodgkin's or lymphoma	____
☐$_{10}$ Kidney	____
☐$_{11}$ Leukemia	____
☐$_{12}$ Liver	____
☐$_{13}$ Lung, bronchus	____
☐$_{14}$ Ovary	____
☐$_{15}$ Pancreas	____
☐$_{16}$ Rectum	____
☐$_{17}$ Skin – Melanoma	____
☐$_{18}$ Skin – Basal or squamous	____
☐$_{19}$ Stomach	____
☐$_{20}$ Thyroid	____
☐$_{21}$ Uterus	____
☐$_{24}$ Fallopian tube	____
☐$_{25}$ Peritoneal	____
☐$_{22}$ Other type not listed *(Specify)*	
_____	____
☐$_{23}$ Don't know	

59. Did any cancer spread (metastasize) beyond its primary site?

☐$_0$ No
☐$_1$ Yes
☐$_9$ Unknown

60. Have you ever taken selective estrogen receptor modulators (SERMs), such as tamoxifen or raloxifene for the **treatment of cancer**?

☐$_0$ No
☐$_1$ Yes
☐$_9$ Unknown

61. How many months did you take SERMs for the **treatment of cancer**?

|_|_|_| Months

62. Are you currently taking SERMs for the **treatment of cancer**?

☐$_0$ No
☐$_1$ Yes

63. If you are not currently taking SERMs for the **treatment of cancer**, approximately how long has it been since SERMs were last taken?

|_|_|_| Months

64. Have you every received radiation therapy for the treatment of cancer?

☐$_0$ No
☐$_1$ Yes
☐$_9$ Unknown

65. What type of cancer and at what age? *(List only primary cancers, that is the place in the body where the cancer started, not where it spread.)*

Primary cancer	Age
☐$_1$ Bladder	__ __
☐$_2$ Bone	__ __
☐$_3$ Brain	__ __
☐$_4$ Breast	__ __
☐$_5$ Cervix	__ __
☐$_6$ Colon	__ __
☐$_7$ Esophagus	__ __
☐$_8$ Head and neck	__ __
☐$_9$ Hodgkin's or lymphoma	__ __
☐$_{10}$ Kidney	__ __
☐$_{11}$ Leukemia	__ __
☐$_{12}$ Liver	__ __
☐$_{13}$ Lung, bronchus	__ __
☐$_{14}$ Ovary	__ __
☐$_{15}$ Pancreas	__ __
☐$_{16}$ Rectum	__ __
☐$_{17}$ Skin – Melanoma	__ __
☐$_{18}$ Skin – Basal or squamous	__ __
☐$_{19}$ Stomach	__ __
☐$_{20}$ Thyroid	__ __
☐$_{21}$ Uterus	__ __
☐$_{24}$ Fallopian tube	__ __
☐$_{25}$ Peritoneal	__ __
☐$_{22}$ Other type not listed *(Specify)* _____	__ __
☐$_{23}$ Don't know	__ __

66. Have you ever received systemic chemotherapy for a malignancy (cancer)?

☐$_0$ No
☐$_1$ Yes
☐$_9$ Unknown

67. What type of cancer and at what age? *(List only primary cancers, that is the place in the body where the cancer started, not where it spread)*

Primary cancer	Age	Agents given
☐$_1$ Bladder	__ __	_____
☐$_2$ Bone	__ __	_____
☐$_3$ Brain	__ __	_____
☐$_4$ Breast	__ __	_____
☐$_5$ Cervix	__ __	_____
☐$_6$ Colon	__ __	_____
☐$_7$ Esophagus	__ __	_____
☐$_8$ Head and neck	__ __	_____
☐$_9$ Hodgkin's or lymphoma	__ __	_____
☐$_{10}$ Kidney	__ __	_____
☐$_{11}$ Leukemia	__ __	_____
☐$_{12}$ Liver	__ __	_____
☐$_{13}$ Lung, bronchus	__ __	_____
☐$_{14}$ Ovary	__ __	_____
☐$_{15}$ Pancreas	__ __	_____
☐$_{16}$ Rectum	__ __	_____
☐$_{17}$ Skin – Melanoma	__ __	_____
☐$_{18}$ Skin – Basal or squamous	__ __	_____
☐$_{19}$ Stomach	__ __	_____
☐$_{20}$ Thyroid	__ __	_____
☐$_{21}$ Uterus	__ __	_____
☐$_{24}$ Fallopian tube	__ __	_____
☐$_{25}$ Peritoneal	__ __	_____
☐$_{22}$ Other type not listed (*Specify)*		
_____	__ __	_____
☐$_{23}$ Don't know	__ __	_____

68. Have you ever had surgery for the treatment/prevention of cancer?

☐$_0$ No
☐$_1$ Yes
☐$_9$ Unknown

69. What type of cancer and at what age? *(List only primary cancers, that is the place in the body where the cancer started, not where it spread)*

Primary cancer	Age
☐$_1$ Bladder	__ __
☐$_2$ Bone	__ __
☐$_3$ Brain	__ __
☐$_4$ Breast	__ __
☐$_5$ Cervix	__ __
☐$_6$ Colon	__ __
☐$_7$ Esophagus	__ __
☐$_8$ Head and neck	__ __
☐$_9$ Hodgkin's or lymphoma	__ __
☐$_{10}$ Kidney	__ __
☐$_{11}$ Leukemia	__ __
☐$_{12}$ Liver	__ __
☐$_{13}$ Lung, bronchus	__ __
☐$_{14}$ Ovary	__ __
☐$_{15}$ Pancreas	__ __
☐$_{16}$ Rectum	__ __
☐$_{17}$ Skin – Melanoma	__ __
☐$_{18}$ Skin – Basal or squamous	__ __
☐$_{19}$ Stomach	__ __
☐$_{20}$ Thyroid	__ __
☐$_{21}$ Uterus	__ __
☐$_{24}$ Fallopian tube	__ __
☐$_{25}$ Peritoneal	__ __
☐$_{22}$ Other type not listed *(Specify)* _____	__ __
☐$_{23}$ Don't know	__ __

Section D

These next questions ask about your lifestyle.

70. Have you smoked at least 100 cigarettes in your lifetime?

☐$_0$ No ⟶ ***If no, go to question 76***
☐$_1$ Yes, and currently smoke
☐$_2$ Yes, and no longer smoke
☐$_9$ Unknown

71. Age started smoking

|_|_| Years old

72. Age stopped smoking

|_|_| Years old

73. In total, about how many years have you smoked (minus periods of non-smoking)?

|_|_| Years

74. Over this period, what is the average number of cigarettes you smoked per day?
(20 cigarettes = 1 pack)

|_|_|_| Cigarettes

Please continue on next page

75. Complete the table below. How many drinks of each type of alcohol listed in the table below do you usually drink, OR have you consumed in the last month?
(Check the appropriate box to indicate the frequency (e.g., per day, week, month))

Alcohol	Number of drinks	Frequency
75a. Beer (1 beer = 12 oz.)	___ ___	☐1 Daily ☐2 Weekly ☐3 Monthly ☐9 Rarely/never drink beer
75b. Wine (1 drink = 5 oz. glass)	___ ___	☐1 Daily ☐2 Weekly ☐3 Monthly ☐9 Rarely/never drink wine
75c. Hard liquor (1 drink = 1.5 oz. (shot))	___ ___	☐1 Daily ☐2 Weekly ☐3 Monthly ☐9 Rarely/never drink hard liquor

76. On average, how much regular (caffeinated) coffee do you drink per day?

☐0 None
☐1 less than 1 cup
☐2 1 cup
☐3 2 cups
☐4 3 cups
☐s More than 3 cups

77. Do you apply, or have you ever applied talc body powder or talc dusting powder to your genital area, underwear, or sanitary napkin at least once a month?

☐0 No
☐1 Yes

78. How frequently do you use, or have you ever used, talc in the genital area each month?

☐0 Never
☐1 1 – 7 times
☐2 8 – 14 times
☐3 15 – 30 times
☐4 More than 30 times
☐9 Unknown

79. How many years have you used talc applied to the genital area?

|__|__| Years

80. Name(s) of products used

81a. _____

81b. _____

81c. _____

81d. _____

81. How many of the following types of x-rays have you had?

Type of x-ray	Number of exposures
81a. Chest x-ray	☐0 None ☐1 1 – 4 ☐2 5 – 9 ☐3 More than 10
81b. Dental x-ray	☐0 None ☐1 1 – 4 ☐2 5 – 9 ☐3 More than 10
81c. Mammogram	☐0 None ☐1 1 – 4 ☐2 5 – 9 ☐3 More than 10

81d. Have you ever had a breast biopsy?

☐0 No
☐1 Yes → 81d1. How many breast biopsies have you had in your lifetime?

|__|__|

☐2 Don't know

Section E

The last 2 questions ask about your family's cancer history.

82. The following questions are about your FEMALE blood relatives (including half-sisters). For each relative, please complete each section. For each disease that you answer "yes" to, please give your best estimate of age when diagnosed in the corresponding box. Please note in the last section "primary cancer" refers to where the cancer started, not where it spread. Please complete the table for **all** FEMALE blood relatives, both with or without cancer, whether alive or deceased.

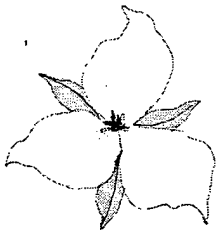
	Is this relative a half-sibling?		Is this individual still living?		Current age or age at death	Ever had ovarian cancer?			Ever had breast cancer?			Ever had colorectal cancer?			Ever had any other primary cancer?		
Relatives	Yes	No	Yes	No		Yes	No	Age	Yes	No	Age	Yes	No	Age	Yes	No	Age
1Mother			☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0	
2Mother's Mother			☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0	
3Father's Mother			☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0	
4Your Sister 1	☐1	☐0	☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0	
4Your Sister 2	☐1	☐0	☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0	
4Your Sister 3	☐1	☐0	☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0	
5Mother's Sister 1	☐1	☐0	☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0	
5Mother's Sister 2	☐1	☐0	☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0	
5Mother's Sister 3	☐1	☐0	☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0	
6Father's Sister 1	☐1	☐0	☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0	
6Father's Sister 2	☐1	☐0	☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0	
6Father's Sister 3	☐1	☐0	☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0	
7Your Daughter 1			☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0	
7Your Daughter 2			☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0	
7Your Daughter 3			☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0	
8Your Niece 1			☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0	
8Your Niece 2			☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0	
8Your Niece 3			☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0	

83. The following questions are about your MALE relatives (including half-brothers). For each relative, please complete each section. For each disease that you answer "yes" to, please give your best estimate of age when diagnosed in the corresponding box. Please note in the last section "primary cancer" refers to where the cancer started, not where it spread. Please complete the table for **all** MALE blood relatives, both with or without cancer, whether alive or deceased.

Relatives	Is this relative a half-sibling?		Is this individual still living?		Current age or age at death	Ever had prostate cancer?			Ever had breast cancer?			Ever had colorectal cancer?			Ever had any other primary cancer?		
	Yes	No	Yes	No		Yes	No	Age	Yes	No	Age	Yes	No	Age	Yes	No	Age
1Father			☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0	
2Mother's Father			☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0	
3Father's Father			☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0	
4Your Brother 1	☐1	☐0	☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0	
4Your Brother 2	☐1	☐0	☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0	
4Your Brother 3	☐1	☐0	☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0	
5Mother's Brother 1	☐1	☐0	☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0	
5Mother's Brother 2	☐1	☐0	☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0	
5Mother's Brother 3	☐1	☐0	☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0	
6Father's Brother 1	☐1	☐0	☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0	
6Father's Brother 2	☐1	☐0	☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0	
6Father's Brother 3	☐1	☐0	☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0	
7Your Son 1			☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0	
7Your Son 2			☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0	
7Your Son 3			☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0	
8Your nephew 1			☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0	
8Your nephew 2			☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0	
8Your nephew 3			☐1	☐2		☐1	☐0		☐1	☐0		☐1	☐0		☐1	☐0	

Instrument 3

Health Status Form



Participant ID #

Breast Cancer Early Discovery Study

Health Status Questionnaire

Version 1.0 [05-21-03]

It is important to our research that you complete this questionnaire on the day that you donate a blood sample, as soon as possible after the blood is drawn. We appreciate your participation in this study, and want you to know that completing this questionnaire is *voluntary*. You are free to skip any of the questions you choose.

1. Date of last menstrual period (*if less than 1 year ago*).

   ___ ___ /___ ___ /___ ___ ___ ___
   month day year

   ❑ Not applicable, no period in the last 12 months

2. In the last 6 months, have your menstrual periods stopped for 3 or more menstrual cycles **for any reason** (e.g. natural menopause, hysterectomy, the removal of both ovaries, or radiation or chemotherapy)?

   ❑$_0$ No
   ❑$_1$ Yes →
   ❑$_9$ Unknown

   2a. At what age did your periods last stop for 3 or more menstrual cycles?

   ___ ___ years old

   2b. Which of the following best describes why your menstrual cycle stopped? *(Please check only one answer)*

   ❑$_0$ Natural menopause (change of life)
   ❑$_1$ Surgery (either uterus and/or ovaries were surgically removed)
   ❑$_2$ Radiation
   ❑$_3$ Medication or drug therapy
   ❑$_4$ Other *(Specify)*_____

3. Is there any reason to believe you are pregnant or have been pregnant in the last 6 months?

   ❑$_0$ No
   ❑$_1$ Yes

4. Have you breastfed a child in the last 6 months?

   ❑$_0$ No
   ❑$_1$ Yes

NEW DIAGNOSIS

5. In the last 6 months have you been diagnosed with a new cancer?

❑$_0$ No
❑$_1$ Yes →

5a. If yes, what was the date of your cancer diagnosis? *(Best guess)*

__ __ / __ __ / __ __ __ __
month day year

5b. If yes, please indicate what kind of cancer you were diagnosed with. List only primary cancers, that is the place in the body where the cancer started, not where it spread. *(Check all that apply)*

❑$_1$ Bladder
❑$_2$ Bone
❑$_3$ Brain
❑$_4$ Breast
❑$_5$ Cervix
❑$_6$ Colon
❑$_7$ Esophagus
❑$_8$ Head and neck
❑$_9$ Hodgkin's or lymphoma
❑$_{10}$ Kidney
❑$_{11}$ Leukemia
❑$_{12}$ Liver
❑$_{13}$ Lung, bronchus
❑$_{14}$ Ovary
❑$_{15}$ Pancreas
❑$_{16}$ Rectum
❑$_{17}$ Skin- Melanoma
❑$_{18}$ Skin- basal or squamous
❑$_{19}$ Stomach
❑$_{20}$ Thyroid
❑$_{21}$ Uterus
❑$_{24}$ Fallopian tube
❑$_{25}$ Peritoneal
❑$_{22}$ Other type not listed
❑$_{23}$ Don't know

6. Are you currently undergoing treatment for cancer?

❑$_0$ No
❑$_1$ Yes →

6a. If yes, what kinds of treatment are you currently receiving? *(Check all that apply)*

❑$_1$ Radiation
❑$_2$ Anti-estrogen therapy using Tamoxifen
❑$_3$ Chemotherapy
❑$_4$ Other
❑$_5$ Don't know

6b. Please provide the name and phone number of the physician who is overseeing your treatment.

Name _____

Phone (__ __ __) __ __ __ - __ __ __ __

7. Please provide the name and address of the hospital where your cancer surgery or biopsy was performed.

Name/Address _____

BREAST PROCEDURES, HOSPITALIZATION AND SURGERY

8. Within the last 6 months, have you had a mammogram?

❑$_0$ No
❑$_1$ Yes →

8a. If yes, please provide the name and phone number of the clinic or hospital where you had your mammogram and the date.

8a1. Date: ___ ___ / ___ ___ / ___ ___ ___ ___
month day year

Name _____

Phone (___ ___ ___) ___ ___ ___ - ___ ___ ___ ___

8a2. Date: ___ ___ / ___ ___ / ___ ___ ___ ___
month day year

Name _____

Phone (___ ___ ___) ___ ___ ___ - ___ ___ ___ ___

8a3. Date: ___ ___ / ___ ___ / ___ ___ ___ ___
month day year

Name _____

Phone (___ ___ ___) ___ ___ ___ - ___ ___ ___ ___

9. In the last 6 months have you had any of the following breast procedures?
(Check all that apply and write in the number of biopsies, if any)

	Left	Right	Both	#
Fine needle aspiration	❑$_1$	❑$_2$	❑$_3$	_____
Core needle biopsy	❑$_1$	❑$_2$	❑$_3$	_____
Open excisional biopsy	❑$_1$	❑$_2$	❑$_3$	_____
Lumpectomy	❑$_1$	❑$_2$	❑$_3$	
Mastectomy	❑$_1$	❑$_2$	❑$_3$	
Radiation therapy	❑$_1$	❑$_2$	❑$_3$	
Reconstruction	❑$_1$	❑$_2$	❑$_3$	
Augmentation/Implants	❑$_1$	❑$_2$	❑$_3$	

10. In the last 6 months, have you been hospitalized overnight?

❑$_0$ No
❑$_1$ Yes →

10a. If yes, please describe why you were in the hospital:

_____

10b. Please provide the name and address of the hospital which provided your care, and the dates of your hospitalization.

10a1.Date: ___ ___ /___ ___ /___ ___ ___ ___
month day year

Name/Address _____

10a2.Date: ___ ___ /___ ___ /___ ___ ___ ___
month day year

Name/Address _____

10a3.Date: ___ ___ /___ ___ /___ ___ ___ ___
month day year

Name/Address _____

11. In the last 6 months have you had outpatient or day surgery?

❑$_0$ No
❑$_1$ Yes →

11a. If yes, please provide the name and address of the clinic or hospital which provided your care, and the date of your procedure.

11a1.Date: ___ ___ /___ ___ /___ ___ ___ ___
month day year

Name/Address _____

11a2.Date: ___ ___ /___ ___ /___ ___ ___ ___
month day year

Name/Address _____

11a3.Date: ___ ___ /___ ___ /___ ___ ___ ___
month day year

Name/Address _____

SYMPTOMS

12. In the last 6 months have you experienced any of the following breast symptoms?

Symptoms/Signs	Check No or Yes	Duration *(Check best answer)* 1 day	2 – 6 days	1 wk – 1 month	More than 1 month
12a. Lump in left breast	❑$_0$ No ❑$_1$ Yes	❑$_1$	❑$_2$	❑$_3$	❑$_4$
12b. Lump in right breast	❑$_0$ No ❑$_1$ Yes	❑$_1$	❑$_2$	❑$_3$	❑$_4$
12c. Nipple discharge in left breast	❑$_0$ No ❑$_1$ Yes	❑$_1$	❑$_2$	❑$_3$	❑$_4$
12d. Nipple discharge in right breast	❑$_0$ No ❑$_1$ Yes	❑$_1$	❑$_2$	❑$_3$	❑$_4$
12e. Pain in left breast	❑$_0$ No ❑$_1$ Yes	❑$_1$	❑$_2$	❑$_3$	❑$_4$
12f. Pain in right breast	❑$_0$ No ❑$_1$ Yes	❑$_1$	❑$_2$	❑$_3$	❑$_4$
12g. Skin changes in right breast	❑$_0$ No ❑$_1$ Yes	❑$_1$	❑$_2$	❑$_3$	❑$_4$
12h. Skin changes in left breast	❑$_0$ No ❑$_1$ Yes	❑$_1$	❑$_2$	❑$_3$	❑$_4$
12i. Other	❑$_0$ No ❑$_1$ Yes	❑$_1$	❑$_2$	❑$_3$	❑$_4$

13. In the last 6 months have you experienced any of the following pelvic or abdominal symptoms?

Symptoms/Signs	Check No or Yes	Duration *(Check best answer)* 1 day	2 – 6 days	1 wk – 1 month	More than 1 month
13a. Bloating	❑$_0$ No ❑$_1$ Yes	❑$_1$	❑$_2$	❑$_3$	❑$_4$
13b. Irregular vaginal bleeding	❑$_0$ No ❑$_1$ Yes	❑$_1$	❑$_2$	❑$_3$	❑$_4$
13c. Abdominal pain	❑$_0$ No ❑$_1$ Yes	❑$_1$	❑$_2$	❑$_3$	❑$_4$
13d. Abdominal discomfort	❑$_0$ No ❑$_1$ Yes	❑$_1$	❑$_2$	❑$_3$	❑$_4$
13e. Abdominal cramps	❑$_0$ No ❑$_1$ Yes	❑$_1$	❑$_2$	❑$_3$	❑$_4$
13f. Urinary changes	❑$_0$ No ❑$_1$ Yes	❑$_1$	❑$_2$	❑$_3$	❑$_4$
13g. Bowel changes	❑$_0$ No ❑$_1$ Yes	❑$_1$	❑$_2$	❑$_3$	❑$_4$
13h. Nausea	❑$_0$ No ❑$_1$ Yes	❑$_1$	❑$_2$	❑$_3$	❑$_4$
13i. Vomiting	❑$_0$ No ❑$_1$ Yes	❑$_1$	❑$_2$	❑$_3$	❑$_4$
13j. Loss of appetite	❑$_0$ No ❑$_1$ Yes	❑$_1$	❑$_2$	❑$_3$	❑$_4$
13k. Low back pain	❑$_0$ No ❑$_1$ Yes	❑$_1$	❑$_2$	❑$_3$	❑$_4$
13l. Other	❑$_0$ No ❑$_1$ Yes	❑$_1$	❑$_2$	❑$_3$	❑$_4$

14. Have you had any infections or cold symptoms in the last 7 days?

❑$_0$ No
❑$_1$ Yes

MEDICATIONS, MEDICAL CONDITIONS AND SCREENING

15. Please indicate when you last used any of the following:

Medication	In the last 24 hours	2-7 days ago	8-30 days ago	More than 30 days ago	Never
15a. Oral contraceptives (birth control pills)	❑$_1$	❑$_2$	❑$_3$	❑$_4$	❑$_5$
15b. Fertility drugs (Clomid, Pergonal, Lupron)	❑$_1$	❑$_2$	❑$_3$	❑$_4$	❑$_5$
15c. Hormone replacement therapy with estrogen or estradiol ONLY (Premarin, Estrace, Estratab, Ortho-est, Ogen, Gynodiol, Cenestin or Alora)	❑$_1$	❑$_2$	❑$_3$	❑$_4$	❑$_5$
15d. Hormone replacement therapy with progestin or progesterone ONLY (Provera, Amen Cycrin, Megace, Curratab, Prometrium or Aygestin)	❑$_1$	❑$_2$	❑$_3$	❑$_4$	❑$_5$
15e. Hormone replacement therapy with both estrogen AND progesterone in the same pill (Prempro. Premphase)	❑$_1$	❑$_2$	❑$_3$	❑$_4$	❑$_5$
15f. Hormone replacement therapy with patches containing female hormones (Estraderm, FemPatch, Alora, Climara Vivelle or CombiPath)	❑$_1$	❑$_2$	❑$_3$	❑$_4$	❑$_5$
15g. Natural hormone replacement therapy using phytoestrogens	❑$_1$	❑$_2$	❑$_3$	❑$_4$	❑$_5$
15h. Acetaminophen (Tylenol)	❑$_1$	❑$_2$	❑$_3$	❑$_4$	❑$_5$
15i. Anti-estrogen therapy (Tamoxifen)	❑$_1$	❑$_2$	❑$_3$	❑$_4$	❑$_5$
15j. Antihistamines, allergy medications, allergy shots (Claritin, Allegra, Clarinex, Zyrtec, Benadryl)	❑$_1$	❑$_2$	❑$_3$	❑$_4$	❑$_5$
15k. Physician prescribed systemic corticosteroids (Rhinocort, Flonase, Prednisone)	❑$_1$	❑$_2$	❑$_3$	❑$_4$	❑$_5$
15l. Aspirin	❑$_1$	❑$_2$	❑$_3$	❑$_4$	❑$_5$
15m. Insulin	❑$_1$	❑$_2$	❑$_3$	❑$_4$	❑$_5$

Medication *(continued)*	**In the last 24 hours**	**2-7 days ago**	**8-30 days ago**	**More than 30 days ago**	**Never**
15n. Non-aspirin pain relievers (Ibuprofen, Aleve, Advil)	❑1	❑2	❑3	❑4	❑5
15o. Antidepressants (Elavil, nortiptyline, Pamelor, Prozac, Sinequan, Zoloft)	❑1	❑2	❑3	❑4	❑5
15p. High Blood Pressure medications (Capoten, Tenormin, Inderal, Verapamil, Lozol, Maxzide, etc.)	❑1	❑2	❑3	❑4	❑5
15q. Anti coagulant (Coumadin, Plavix, Ticlid)	❑1	❑2	❑3	❑4	❑5
15r. Cardiac/Heart medications (Adenocard, Norvasc, Capoten, Isordil, Tenormin, Bumex, Lanoxin, Cozaar, etc)	❑1	❑2	❑3	❑4	❑5
15s. NSAIDS (Motrin, Naprosyn, Clinoril, Relafen, Indocin, Lodine, Voltaren, Feldene, etc)	❑1	❑2	❑3	❑4	❑5
15t. Cholesterol lowering drugs (Lipitor, Zocor, Pravachol, Leschol, Zetia, Niacin, etc)	❑1	❑2	❑3	❑4	❑5
15u. Hypothyroid medications (Synthroid, Euthyrox)	❑1	❑2	❑3	❑4	❑5
15v. Hyperthyroid medications (PTU, methimazole)	❑1	❑2	❑3	❑4	❑5
15w. Other *(Specify)*_____	❑1	❑2	❑3	❑4	❑5
Tobacco	❑1	❑2	❑3	❑4	❑5
15x. Cigarettes	❑1	❑2	❑3	❑4	❑5
Alcohol	❑1	❑2	❑3	❑4	❑5
15y. Alcoholic beverages (beer, wine, hard liquor)	❑1	❑2	❑3	❑4	❑5
Immunizations	❑1	❑2	❑3	❑4	❑5
15z. Immunizations (tetanus, flu shot or travel vaccination)	❑1	❑2	❑3	❑4	❑5

16. Do you have any of the following medical conditions? *(Check all that apply)*

❑$_0$ No
❑$_1$ Yes →

16a.

❑$_1$ Hypertension	❑$_{12}$ Ulcerative colitis	❑$_{21}$ Hypothyroidism
❑$_2$ Arthritis	❑$_{13}$ Blood clots	❑$_{22}$ Bone disorders
❑$_3$ Hyperthyroidism	❑$_{14}$ Polyps	❑$_{23}$ Chronic hepatitis
❑$_4$ Diabetes	❑$_{15}$ Leukemia/lymphoma	❑$_{24}$ Bleeding problem
❑$_5$ Tuberculosis	❑$_{16}$ Cardiac (Heart)	❑$_{25}$ Gall bladder disease
❑$_6$ Renal disease	❑$_{17}$ Gastro-Intestinal (GI) Bleeding	❑$_{26}$ Emphysema/Asthma
❑$_7$ HIV/AIDS		❑$_{27}$ Fibrocystic disease
❑$_8$ Pancreatitis	❑$_{18}$ Pneumonia	❑$_{28}$ Other _____
❑$_9$ Ulcers	❑$_{19}$ Allergies	_____
❑$_{10}$ Crohns disease	❑$_{20}$ Acute hepatitis	_____
❑$_{11}$ Cirrhosis	❑$_{21}$ Diverticulitis	

ENVIRONMENTAL HISTORY

17. When was your last meal prior to donating your most recent study blood sample?

Time: ___ ___ : ___ ___ am pm *(Circle one)* Date: ❑ Today *or*

___ ___ / ___ ___ / ___ ___ ___ ___
month day year

18. When did you donate your most recent study blood sample?

Time: ___ ___ : ___ ___ am pm *(Circle one)* Date: ❑ Today *or*

___ ___ / ___ ___ / ___ ___ ___ ___
month day year

19. When did you complete this questionnaire?

Time: ___ ___ : ___ ___ am pm *(Circle one)* Date: ❑ Today *or*

___ ___ / ___ ___ / ___ ___ ___ ___
month day year

Thank you for completing this questionnaire!

Instrument 4

Patient Clinical Status at Enrollment

BREAST CANCER EARLY DISCOVERY STUDY: PATIENT CLINICAL STATUS AT ENROLLMENT

(to be completed after pathology results are obtained)

UPN_____ **Form Completed By:** _____

Today's Date: ____ / ____ / ____

PATIENT INFORMATION

First Name_____ Last Name_____ Middle Initial_____

Social Security Number ___ ___ ___-___ ___-___ ___ ___ ___ Date of Birth ___/___/___ (month / day / year)

Street Address_____ City _____ State_____ Zip_____

CLINICAL INFORMATION *(To be abstracted by study personnel)*

1. Reason for biopsy/surgical procedure:

- ☐0 Breast mass detected
- ☐1 Abnormal mammogram
- ☐2 Abnormal ultrasound
- ☐3 Abnormal MRI
- ☐4 Deceased
- ☐5 Nipple discharge
- ☐6 Other_____
- ☐99 Unknown

2. Location of primary tumor:

- ☐0 Upper outer quadrant (UOQ)
- ☐1 Upper inner quadrant (UIQ)
- ☐2 Lower outer quadrant (LOQ)
- ☐3 Lower inner quadrant (LIQ)
- ☐4 Central
- ☐5 Axillia
- ☐6 Other _____
- ☐99 Unknown

3. Initial procedure performed:

☐0 Fine Needle Aspiration (FNA)

☐1 Core Biopsy → **3a. Was U/S used?**

- ☐0 No
- ☐1 Yes
- ☐99 Unknown

☐3 Mammotome Biopsy → **3b. Type of biopsy:**

- ☐0 Stereotactic (mammogram guided) biopsy
- ☐1 Hand held

↓

3bi. Was U/S used?

- ☐0 No
- ☐1 Yes
- ☐99 Unknown

☐3 Surgical Biopsy → **3c. Was there a concurrent lymph node biopsy?**

- ☐0 No
- ☐1 Yes
- ☐99 Unknown

☐4 Lumpectomy

☐5 Mastectomy

☐6 Other *(specify)*_____

☐99 Unknown

Continued on next page

4. **Were lymph nodes removed?**

☐$_0$ No
☐$_1$ Yes
☐$_{99}$ Unknown

5. **Were any lymph nodes positive for metastases?**

☐$_0$ No
☐$_1$ Yes
☐$_{99}$ Unknown

6. **Other tests performed to find metastases.** *(Check all that apply)*

☐$_0$ CT chest
☐$_1$ CT abdomen/pelvis
☐$_2$ Bone Scan
☐$_3$ PET Scan
☐$_4$ MRI
☐$_5$ Neotech
☐$_6$ Chest X-Ray (CXR)
☐$_7$ Blood tests
☐$_8$ Other
☐$_{99}$ Unknown

7. **Were any of the following metastases identified?** *(Check all that apply)*

☐$_0$ Bone
☐$_1$ Liver
☐$_2$ Lungs
☐$_3$ Brain
☐$_4$ Other
☐$_{99}$ Unknown

Instrument 5

Clinical Status Follow Up

BREAST CANCER EARLY DISCOVERY STUDY
Clinical Status Follow Up

PATIENT INFORMATION

UPN_____

First Name_____ Last Name_____ Middle Initial_____

Social Security Number ___ ___ ___-___ ___-___ ___ ___ ___ Date of Birth ___ ___/___ ___/___ ___ ___ ___
month day year

Street Address_____ City _____ State_____ Zip_____

CLINICAL INFORMATION *(To be abstracted by study personnel)*

1. Today's date

___ ___/___ ___/___ ___ ___ ___
month day year

2. Clinical status of participant at time of follow up

- ☐0 Alive, No evidence of disease (NED)
- ☐1 Alive with persistent disease
- ☐2 Alive with progressive disease
- ☐3 Alive with recurrence
- ☐4 Deceased → **2a. Date of death**

  ___ ___/___ ___/___ ___ ___ ___ ☐999 Unknown
  month day year

  2b. Disease status at time of death *(Check one)*
  - ☐0 NED
  - ☐1 Persistent disease
  - ☐2 Progression
  - ☐3 Recurrence
  - ☐999 Unknown

3. Please indicate if the participant has undergone any of the following procedures in the past XXX months. *(Check all that apply)*

- ☐0 Fine Needle Aspiration → **3a. Reason for the procedure** *(Check all that apply)*
  - ☐0 Breast mass detected
  - ☐1 Abnormal mammogram
  - ☐2 Abnormal ultrasound
  - ☐3 Abnormal MRI
  - ☐4 Deceased
  - ☐5 Nipple discharge
  - ☐6 Other:_____
  - ☐999 Unknown

☐1 Core Biopsy → **3b. Reason for the procedure** *(Check all that apply)*

- ☐0 Breast mass detected
- ☐1 Abnormal mammogram
- ☐2 Abnormal ultrasound
- ☐3 Abnormal MRI
- ☐4 Deceased
- ☐5 Nipple discharge
- ☐6 Other:_____
- ☐999 Unknown

3c. Was U/S used?

- ☐0 No
- ☐1 Yes
- ☐999 Unknown

☐3 Mammotome Biopsy → **3d. Reason for the procedure** *(Check all that apply)*:

- ☐0 Breast mass detected
- ☐1 Abnormal mammogram
- ☐2 Abnormal ultrasound
- ☐3 Abnormal MRI
- ☐4 Deceased
- ☐5 Nipple discharge
- ☐6 Other:_____
- ☐999 Unknown

3e. Type of biopsy

- ☐0 Stereotactic (mammogram guided) biopsy
- ☐1 Hand held

→ **3ei. Was U/S used?**

- ☐0 No
- ☐1 Yes
- ☐999 Unknown

☐3 Surgical Biopsy → **3f. Reason for the procedure** *(Check all that apply)*

- ☐0 Breast mass detected
- ☐1 Abnormal mammogram
- ☐2 Abnormal ultrasound
- ☐3 Abnormal MRI
- ☐4 Deceased
- ☐5 Nipple discharge
- ☐6 Other:_____
- ☐999 Unknown

3g. Was there a concurrent lymph node biopsy?

- ☐0 No
- ☐1 Yes
- ☐999 Unknown

☐4 Lumpectomy → **3h. Reason for the procedure** *(Check all that apply)*

- ☐0 Breast mass detected
- ☐1 Abnormal mammogram
- ☐2 Abnormal ultrasound
- ☐3 Abnormal MRI
- ☐4 Deceased
- ☐5 Nipple discharge
- ☐6 Other:_____
- ☐999 Unknown

☐5 Mastectomy → **3i. Reason for the procedure** *(Check all that apply)*

- ☐0 Breast mass detected
- ☐1 Abnormal mammogram
- ☐2 Abnormal ultrasound
- ☐3 Abnormal MRI
- ☐4 Deceased
- ☐5 Nipple discharge
- ☐6 Other:_____
- ☐999 Unknown

☐6 Other:_____ → **3j. Reason for the procedure** *(Check all that apply)*

- ☐0 Breast mass detected
- ☐1 Abnormal mammogram
- ☐2 Abnormal ultrasound
- ☐3 Abnormal MRI
- ☐4 Deceased
- ☐5 Nipple discharge
- ☐6 Other:_____
- ☐999 Unknown

☐999 Unknown

IF THE PARTICIPANT HAS BEEN DIAGNOSED WITH CANCER DURING THE COURSE OF THE STUDY, PLEASE COMPLETE THE TREATMENT SECTION OF THIS FORM.

Please complete the following only if the participant has been diagnosed with cancer during the course of the study UPN_____

TREATMENT

4. **Date of most recent cancer diagnosis:** ___ ___/___ ___/___ ___ ___ ___
   month day year

5. **Type of cancer participant was diagnosed with:**

☐1 Bladder	☐10 Kidney	☐19 Stomach
☐2 Bone	☐11 Leukemia	☐20 Thyroid
☐3 Brain	☐12 Liver	☐21 Uterus
☐4 Breast	☐13 Lung, bronchus	☐22 Fallopian Tube
☐5 Cervix	☐14 Ovary	☐23 Peritoneal
☐6 Colon	☐15 Pancreas	☐24 Other: _____
☐7 Esophagus	☐16 Rectum	☐999 Unknown
☐8 Head and neck	☐17 Skin–melanoma	
☐9 Hodgkin's or lymphoma	☐18 Skin–basal or Squamous	

6. **Did the participant receive radiation therapy following diagnosis?**

   ☐0 No ☐1 Yes

   6a. Duration of radiation therapy:

   ___ ___/___ ___ ___ ___ to ___ ___/___ ___ ___ ___
   month year month year

   ☐999 Unknown

7. **Did the participant receive chemotherapy or hormonal therapy following diagnosis?**

   ☐0 No ☐1 Yes

   7a. Please complete the following information about treatment:

   REGIMEN NUMBER:_____ **Frequency:**_____

   Chemotherapy and Hormonal Agents (*check all that apply):*

☐ 5-FU	☐ Etoposide (VP-16)	☐ Tamoxifen
☐ Doxorubicin (Adriamycin)	☐ Gemcitabine (Gemzar)	☐ Topotecan
☐ Arimidex	☐ Herceptin	☐ Toremifine
☐ BMT	☐ LH/RH agonist	☐ Vinblastine (Velban)
☐ Carboplatinum	☐ Megace	☐ Vinorelbine (Navelbine)
☐ Cis-Platinum	☐ Methotrexate	☐ Xoloda
☐ Clyclophosphamide (Cytoxan)	☐ Mitoxantrone	☐ Topotecan
☐ Docetaxel (Taxotere)	☐ PBSC	
☐ Doxil	☐ Paclitaxel (Taxol)	

   Start date _____/_____/_____ **Stop date** _____/_____/_____

CONTINUED ON NEXT PAGE: ☐0 No ☐1 Yes

Photocopy this sheet if needed to record all treatment cycles **UPN**______________

REGIMEN NUMBER:______ **Frequency:**________________________

Chemotherapy and Hormonal Agents (*check all that apply):*

- ☐ 5-FU
- ☐ Doxorubicin (Adriamycin)
- ☐ Arimidex
- ☐ BMT
- ☐ Carboplatinum
- ☐ Cis-Platinum
- ☐ Clyclophosphamide (Cytoxan)
- ☐ Docetaxel (Taxotere)
- ☐ Doxil
- ☐ Etoposide (VP-16)
- ☐ Gemcitabine (Gemzar)
- ☐ Herceptin
- ☐ LH/RH agonist
- ☐ Megace
- ☐ Methotrexate
- ☐ Mitoxantrone
- ☐ PBSC
- ☐ Paclitaxel (Taxol)
- ☐ Tamoxifen
- ☐ Topotecan
- ☐ Toremifine
- ☐ Vinblastine (Velban)
- ☐ Vinorelbine (Navelbine)
- ☐ Xoloda
- ☐ Topotecan

Start date _____/_____/_____ **Stop date** _____/_____/_____

REGIMEN NUMBER:______ **Frequency:**________________________

Chemotherapy and Hormonal Agents (*check all that apply):*

- ☐ 5-FU
- ☐ Doxorubicin (Adriamycin)
- ☐ Arimidex
- ☐ BMT
- ☐ Carboplatinum
- ☐ Cis-Platinum
- ☐ Clyclophosphamide (Cytoxan)
- ☐ Docetaxel (Taxotere)
- ☐ Doxil
- ☐ Etoposide (VP-16)
- ☐ Gemcitabine (Gemzar)
- ☐ Herceptin
- ☐ LH/RH agonist
- ☐ Megace
- ☐ Methotrexate
- ☐ Mitoxantrone
- ☐ PBSC
- ☐ Paclitaxel (Taxol)
- ☐ Tamoxifen
- ☐ Topotecan
- ☐ Toremifine
- ☐ Vinblastine (Velban)
- ☐ Vinorelbine (Navelbine)
- ☐ Xoloda
- ☐ Topotecan

Start date _____/_____/_____ **Stop date** _____/_____/_____

REGIMEN NUMBER:______ **Frequency:**________________________

Chemotherapy and Hormonal Agents (*check all that apply):*

- ☐ 5-FU
- ☐ Doxorubicin (Adriamycin)
- ☐ Arimidex
- ☐ BMT
- ☐ Carboplatinum
- ☐ Cis-Platinum
- ☐ Clyclophosphamide (Cytoxan)
- ☐ Docetaxel (Taxotere)
- ☐ Doxil
- ☐ Etoposide (VP-16)
- ☐ Gemcitabine (Gemzar)
- ☐ Herceptin
- ☐ LH/RH agonist
- ☐ Megace
- ☐ Methotrexate
- ☐ Mitoxantrone
- ☐ PBSC
- ☐ Paclitaxel (Taxol)
- ☐ Tamoxifen
- ☐ Topotecan
- ☐ Toremifine
- ☐ Vinblastine (Velban)
- ☐ Vinorelbine (Navelbine)
- ☐ Xoloda
- ☐ Topotecan

Start date _____/_____/_____ **Stop date** _____/_____/_____

CONTINUED ON NEXT PAGE: ☐$_0$ No ☐$_1$ Yes

Instrument 6

Participant Pathology at Diagnosis

BREAST CANCER EARLY DISCOVERY STUDY
Participant Pathology at Diagnosis

UPN: _____

Today's Date: ____ / ____ / ____ Form completed by:_____

SECTION A: Patient Information

First Name_____ Last Name_____ Middle Initial____

Social Security Number ___ ___ ___-___ ___-___ ___ ___ ___ Date of Birth ___(month)/___(day)/___ ___(year)

Street Address_____ City _____ State____ Zip_____

SECTION B: Specimen Collection Information

1. **Specimen was collected from the following procedure:**
   - ☐1 Stereotactic biopsy
   - ☐2 Open excisional biopsy
   - ☐3 Fine needle aspiration
   - ☐4 Core needle biopsy
   - ☐5 Vacuum assisted biopsy
   - ☐6 Large core biopsy
   - ☐7 Lumpectomy
   - ☐8 Mastectomy
   - ☐9 Other *(Specify)* _____

2. **Please indicate laterality of the procedure:**
   - ☐1 Left breast
   - ☐2 Right breast
   - ☐999 Unknown

SECTION C: Lymph Node Pathology

1. **Total number of lymph nodes identified (removed):**

   ___ ___

2. **Technique used to evaluate lymph nodes:**
   - ☐1 H & E
   - ☐2 HC
   - ☐3 Other *(Specify)* _____
   - ☐999 Unknown

3. Was a Sentinal lymph node identified?

☐$_0$ No
☐$_1$ Yes → **3a. Technique used:**
☐$_{999}$ Unknown

- ☐$_1$ Lympazurin Blue Dye
- ☐$_2$ Methylene Blue Dye
- ☐$_3$ Tc99 sulfer colloid
- ☐$_4$ Other
- ☐$_5$ Unknown
- ☐$_6$ Other *(Specify)* _____
- ☐$_{999}$ Unknown

3b. Number of sentinal lymph nodes identified:

___ ___

4. Were lymph node metastases present?

☐$_0$ No
☐$_1$ Yes → **4a. Total number of H&E positive lymph nodes:**
☐$_{999}$ Unknown

___ ___

4b. Size of largest metastasis:

___ ___ mm

4c. Were metastases only detected with IHC?

- ☐$_1$ No
- ☐$_2$ Yes
- ☐$_{999}$ Unknown

4d Other characteristics. *(Check all that apply)*

- ☐$_1$ Extension through capsule
- ☐$_2$ Matted or fixed (immobile)

SECTION D: Marker Status

1. Estrogen receptor status at dx. *(Check one)*

- ☐$_1$ Negative
- ☐$_2$ Positive
- ☐$_3$ Indeterminate
- ☐$_4$ Test Not Performed
- ☐$_{99}$ Unknown

2. Progesterone receptor status at dx. *(Check one)*

- ☐$_1$ Negative
- ☐$_2$ Positive
- ☐$_3$ Indeterminate
- ☐$_4$ Test Not Performed
- ☐$_{99}$ Unknown

3. **Her2/neu overexpression at dx.** *(Check one)*

☐$_1$ Negative (0-1+)
☐$_2$ Low Positive (2+)
☐$_3$ Strong Positive (3+)
☐$_4$ Test Not Performed
☐$_{99}$ Unknown

4. **Her2/neu marker test performed.** *(Check one)*

☐$_1$ IHC (Hercept)
☐$_2$ FISH
☐$_3$ ELISA
☐$_4$ Other *(Specify)* _____
☐$_5$ Test Not Performed
☐$_{99}$ Unknown

5. **KI-67 at dx.** *(Check one)*

☐$_1$ Low
☐$_2$ High
☐$_3$ Indeterminate
☐$_4$ Test Not Performed
☐$_{99}$ Unknown

6. **Other tumor markers at dx.** *(Check all that apply)*

Marker	Not Done	Done	Result
DNA Ploidy	☐$_0$	☐$_1$	_____
S phase	☐$_0$	☐$_1$	_____
P53	☐$_0$	☐$_1$	_____
CEA	☐$_0$	☐$_1$	_____
CA 27-29	☐$_0$	☐$_1$	_____

Please continue on next page

SECTION E. Tissue Characteristics

Please duplicate all of section E of this form for each histologic cell type present.

1. Histology

☐1 Predominant
☐2 Other cell type *(number)*: ____

2. Date histology identified

____ ____ / ____ ____ / ____ ____ ____ ____
month day year

3. Please check if histology is INVASIVE ☐

3a. Invasive histology type

☐1 Epithelial → ☐1 Ductal
☐2 Lobular
☐3 Medullary
☐4 Tubular → ☐0 > 90% tubular
☐1 < 90% tubular *(Specify other cell types)* _____
☐5 Mucinous → ☐0 > 75% mucinous
☐1 < 75% mucinous *(Specify other cell types)* _____
☐6 Papillary
☐7 Adenoid cystic
☐8 Metaplastic
☐9 Squamous cell

☐2 Stromal → ☐1 Phylloides
☐2 Sarcoma *(Specify type)* _____

☐3 Other *(Specify)*
_____
_____

☐99 Unknown

3b. Grade

☐1 Low nuclear grade
☐2 Intermediate nuclear grade
☐3 High nuclear grade
☐99 Unknown

3c. Is there lymphatic or vascular invasion?

☐1 No
☐2 Yes
☐99 Unknown

SECTION E. Tissue Characteristics *(continued)*

4. Please check if histology is IN SITU ☐

4a. In situ histology type
- ☐1 Ductal (DCIS)
- ☐2 Lobular (LCIS)
- ☐3 Other *(Specify)*
- ☐99 Unknown

4b. Grade
- ☐1 Low nuclear grade
- ☐2 Intermediate nuclear grade
- ☐3 High nuclear grade
- ☐99 Unknown

4c. Is necrosis present?
- ☐1 No
- ☐2 Yes
- ☐99 Unknown

4d. Is there micro-invasion?
- ☐1 No
- ☐2 Yes
- ☐99 Unknown

5. Please check if histology is ATYPIA ☐

5a. Atypia histology type
- ☐1 Ductal hyperplasia with atypia (ADH)
- ☐2 Lobular hyperplasia with atypia (ALH)
- ☐3 Intraductal papilloma with atypia
- ☐4 Columnar cell change with atypia
- ☐5 Other *(Specify)* _____
- ☐99 Unknown

6. Please check if histology is BENIGN ☐

6a. Benign histology type
- ☐1 Ductal hyperplasia (without atypia)
- ☐2 Sclerosing adenosis
- ☐3 Fibroadenoma
- ☐4 Cellular fibroadenoma
- ☐5 Intraductal papilloma
- ☐6 Radial scar
- ☐7 Columnar cell change (without atypia)
- ☐8 Cyst
- ☐9 Other *(Specify)* _____
- ☐99 Unknown

7. Tumor size:

7a. Gross ___ ___ ___ . ___ cm

7b. Microscopic ___ ___ ___ . ___ cm

SECTION E. Tissue Characteristics *(continued)*

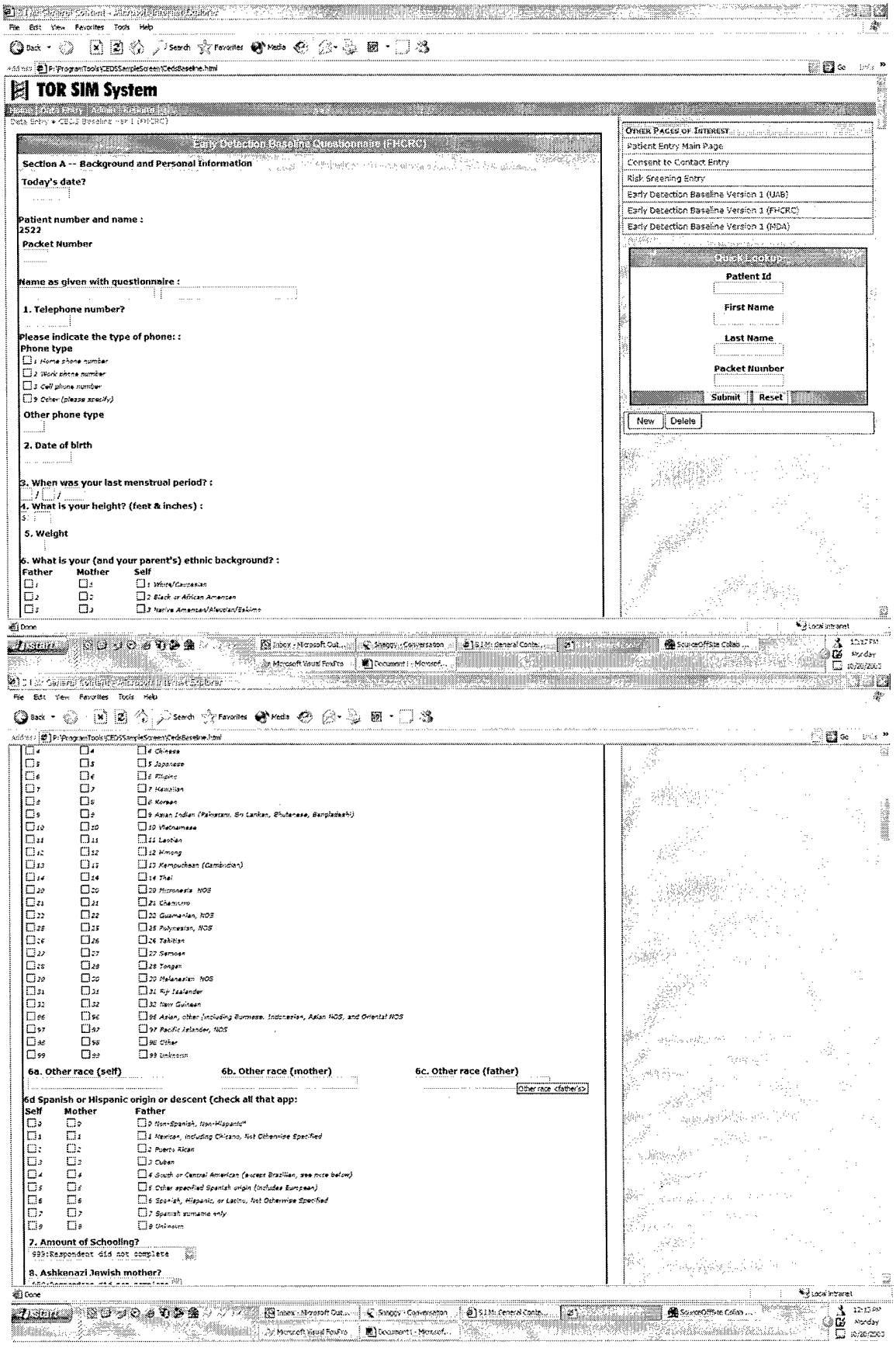
8. Margin involvement

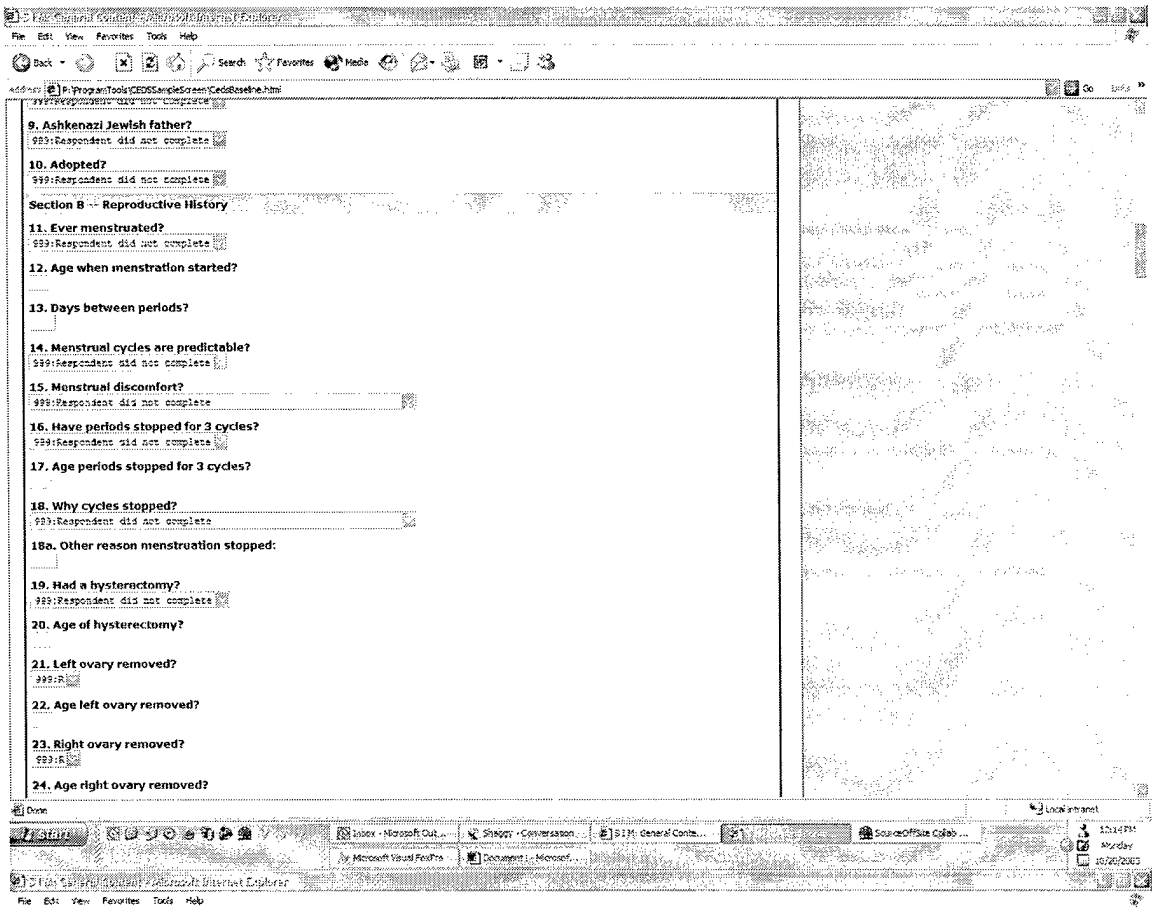
- ☐1 < than 1mm
- ☐2 From 1mm to 10mm
- ☐3 > 10mm
- ☐4 Involved, NOS
- ☐5 Not involved, NOS
- ☐99 Unknown

9. Other Classifications (complete for predominant histology only)

- ☐1 Inflammatory CA
- ☐2 Paget's Disease
- ☐3 Other
- ☐99 Unknown

Appendix F
Baseline Data Entry
(Screen Shots)


TOR SIM System
Early Detection Baseline Questionnaire (FHCRC)
Section A -- Background and Personal Information
Today's date?
Patient number and name :
2522
Packet Number
Name as given with questionnaire :
1. Telephone number?
Please indicate the type of phone: :
Phone type
1 Home phone number
2 Work phone number
3 Cell phone number
9 Other (please specify)
Other phone type
2. Date of birth
3. When was your last menstrual period? :
4. What is your height? (feet & inches) :
5. Weight
6. What is your (and your parent's) ethnic background? :
Father
Mother
Self
1 White/Caucasian
2 Black or African American
3 Native American/Aleutian/Eskimo
Other Pages of Interest
Patient Entry Main Page
Consent to Contact Entry
Risk Screening Entry
Early Detection Baseline Version 1 (UAB)
Early Detection Baseline Version 1 (FHCRC)
Early Detection Baseline Version 1 (MDA)
Quick Lookup
Patient Id
First Name
Last Name
Packet Number
Submit
Reset
New
Delete
4 Chinese
5 Japanese
6 Filipino
7 Hawaiian
8 Korean
9 Asian Indian (Pakistani, Sri Lankan, Bhutanese, Bangladeshi)
10 Vietnamese
11 Laotian
12 Hmong
13 Kampuchean (Cambodian)
14 Thai
20 Micronesia, NOS
21 Chamorro
22 Guamanian, NOS
25 Polynesian, NOS
26 Tahitian
27 Samoan
28 Tongan
30 Melanesian, NOS
31 Fiji Islander
32 New Guinean
96 Asian, other (including Burmese, Indonesian, Asian NOS, and Oriental NOS
97 Pacific Islander, NOS
98 Other
99 Unknown
6a. Other race (self)
6b. Other race (mother)
6c. Other race (father)
Other race (father's)
6d Spanish or Hispanic origin or descent (check all that app:
Self
Mother
Father
0 Non-Spanish, Non-Hispanic
1 Mexican, including Chicano, Not Otherwise Specified
2 Puerto Rican
3 Cuban
4 South or Central American (except Brazilian, see note below)
5 Other specified Spanish origin (includes European)
6 Spanish, Hispanic, or Latino, Not Otherwise Specified
7 Spanish surname only
9 Unknown
7. Amount of Schooling?
999:Respondent did not complete
8. Ashkenazi Jewish mother?



9. Ashkenazi Jewish father?
999:Respondent did not complete

10. Adopted?
999:Respondent did not complete

Section B -- Reproductive History

11. Ever menstruated?
999:Respondent did not complete

12. Age when menstration started?

13. Days between periods?

14. Menstrual cycles are predictable?
999:Respondent did not complete

15. Menstrual discomfort?
999:Respondent did not complete

16. Have periods stopped for 3 cycles?
999:Respondent did not complete

17. Age periods stopped for 3 cycles?

18. Why cycles stopped?
999:Respondent did not complete

18a. Other reason menstruation stopped:

19. Had a hysterectomy?
999:Respondent did not complete

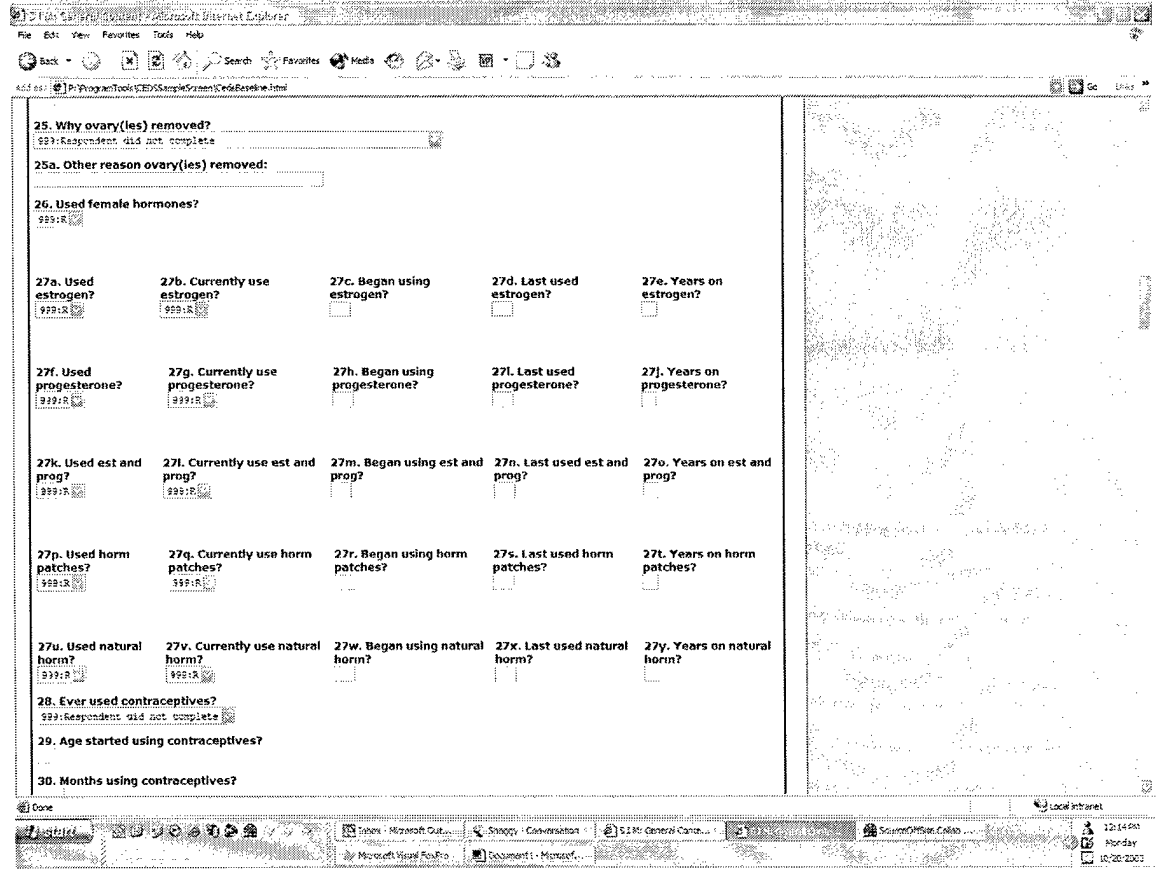
20. Age of hysterectomy?

21. Left ovary removed?
999:R

22. Age left ovary removed?

23. Right ovary removed?
999:R

24. Age right ovary removed?



25. Why ovary(ies) removed?
999:Respondent did not complete

25a. Other reason ovary(ies) removed:

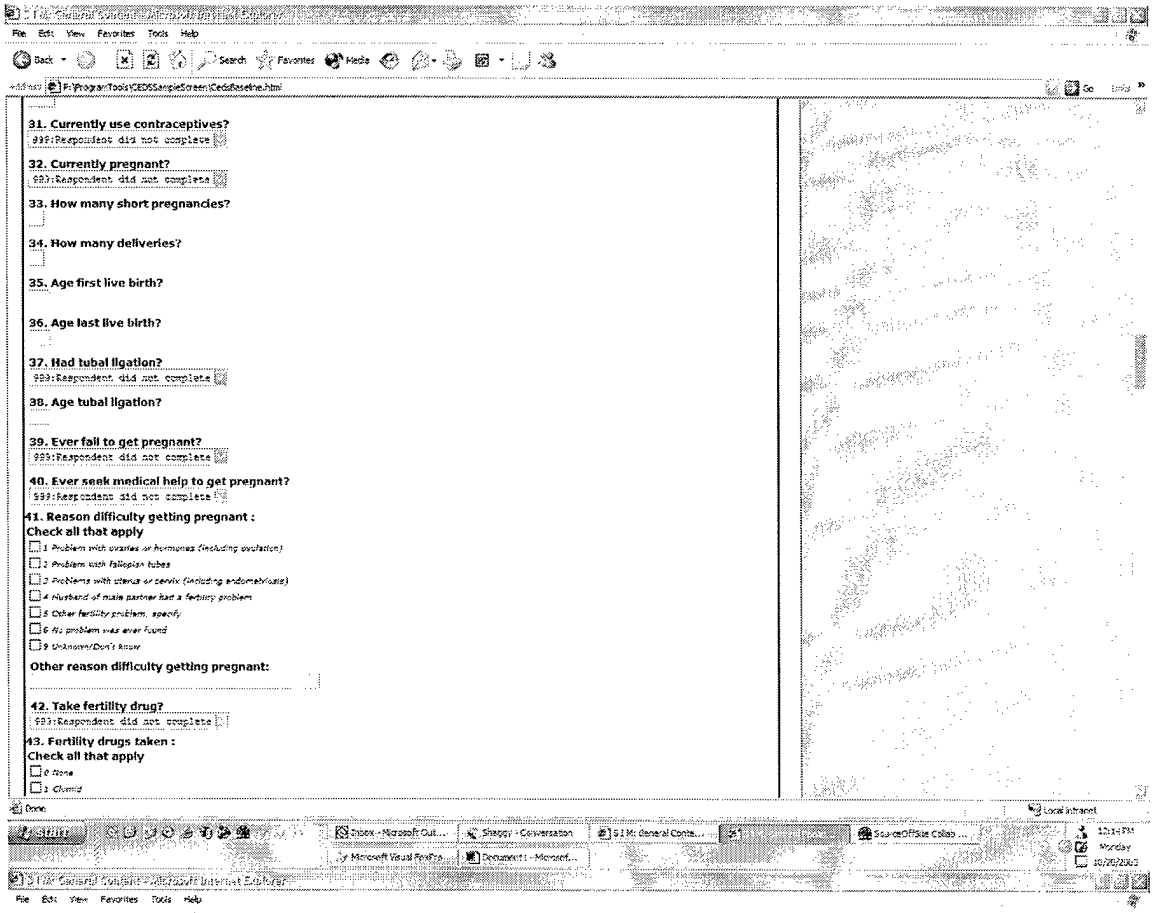
26. Used female hormones?
999:R

27a. Used estrogen?	27b. Currently use estrogen?	27c. Began using estrogen?	27d. Last used estrogen?	27e. Years on estrogen?
999:R	999:R			
27f. Used progesterone?	**27g. Currently use progesterone?**	**27h. Began using progesterone?**	**27i. Last used progesterone?**	**27j. Years on progesterone?**
999:R	999:R			
27k. Used est and prog?	**27l. Currently use est and prog?**	**27m. Began using est and prog?**	**27n. Last used est and prog?**	**27o. Years on est and prog?**
999:R	999:R			
27p. Used horm patches?	**27q. Currently use horm patches?**	**27r. Began using horm patches?**	**27s. Last used horm patches?**	**27t. Years on horm patches?**
999:R	999:R			
27u. Used natural horm?	**27v. Currently use natural horm?**	**27w. Began using natural horm?**	**27x. Last used natural horm?**	**27y. Years on natural horm?**
999:R	999:R			

28. Ever used contraceptives?
999:Respondent did not complete

29. Age started using contraceptives?

30. Months using contraceptives?



31. Currently use contraceptives?
999:Respondent did not complete

32. Currently pregnant?
999:Respondent did not complete

33. How many short pregnancies?

34. How many deliveries?

35. Age first live birth?

36. Age last live birth?

37. Had tubal ligation?
999:Respondent did not complete

38. Age tubal ligation?

39. Ever fail to get pregnant?
999:Respondent did not complete

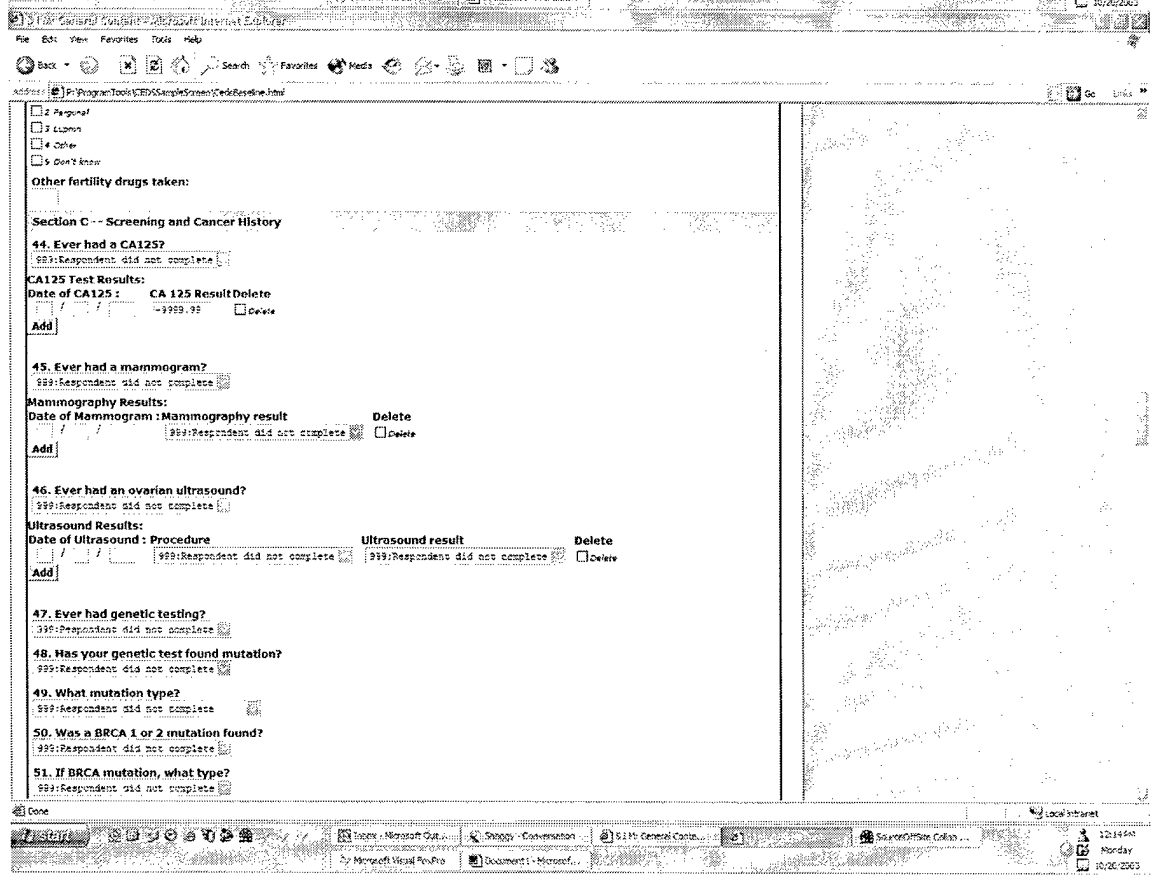
40. Ever seek medical help to get pregnant?
999:Respondent did not complete

41. Reason difficulty getting pregnant :
Check all that apply
1 Problem with ovaries or hormones (including ovulation)
2 Problem with fallopian tubes
3 Problems with uterus or cervix (including endometriosis)
4 Husband of male partner had a fertility problem
5 Other fertility problem, specify
6 No problem was ever found
9 Unknown/Don't know

Other reason difficulty getting pregnant:

42. Take fertility drug?
999:Respondent did not complete

43. Fertility drugs taken :
Check all that apply
0 None
1 Clomid



2 Pergonal
3 Lupron
4 Other
5 Don't know

Other fertility drugs taken:

Section C -- Screening and Cancer History

44. Ever had a CA125?
999:Respondent did not complete

CA125 Test Results:

Date of CA125 :	CA 125 Result	Delete
/ /	-9999.99	Delete

Add

45. Ever had a mammogram?
999:Respondent did not complete

Mammography Results:

Date of Mammogram :	Mammography result	Delete
/ /	999:Respondent did not complete	Delete

Add

46. Ever had an ovarian ultrasound?
999:Respondent did not complete

Ultrasound Results:

Date of Ultrasound :	Procedure	Ultrasound result	Delete
/ /	999:Respondent did not complete	999:Respondent did not complete	Delete

Add

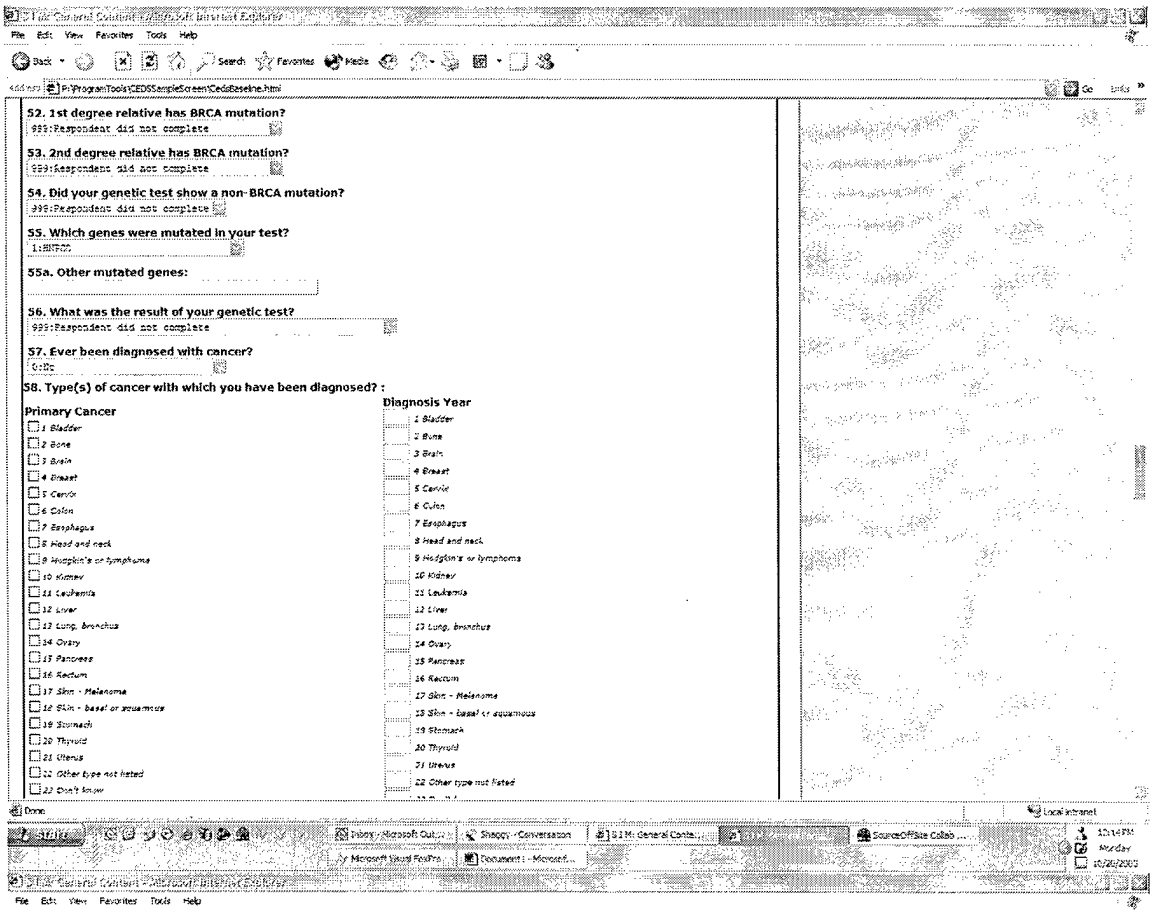
47. Ever had genetic testing?
999:Respondent did not complete

48. Has your genetic test found mutation?
999:Respondent did not complete

49. What mutation type?
999:Respondent did not complete

50. Was a BRCA 1 or 2 mutation found?
999:Respondent did not complete

51. If BRCA mutation, what type?
999:Respondent did not complete



52. 1st degree relative has BRCA mutation?
999:Respondent did not complete

53. 2nd degree relative has BRCA mutation?
999:Respondent did not complete

54. Did your genetic test show a non-BRCA mutation?
999:Respondent did not complete

55. Which genes were mutated in your test?
1:MMR2

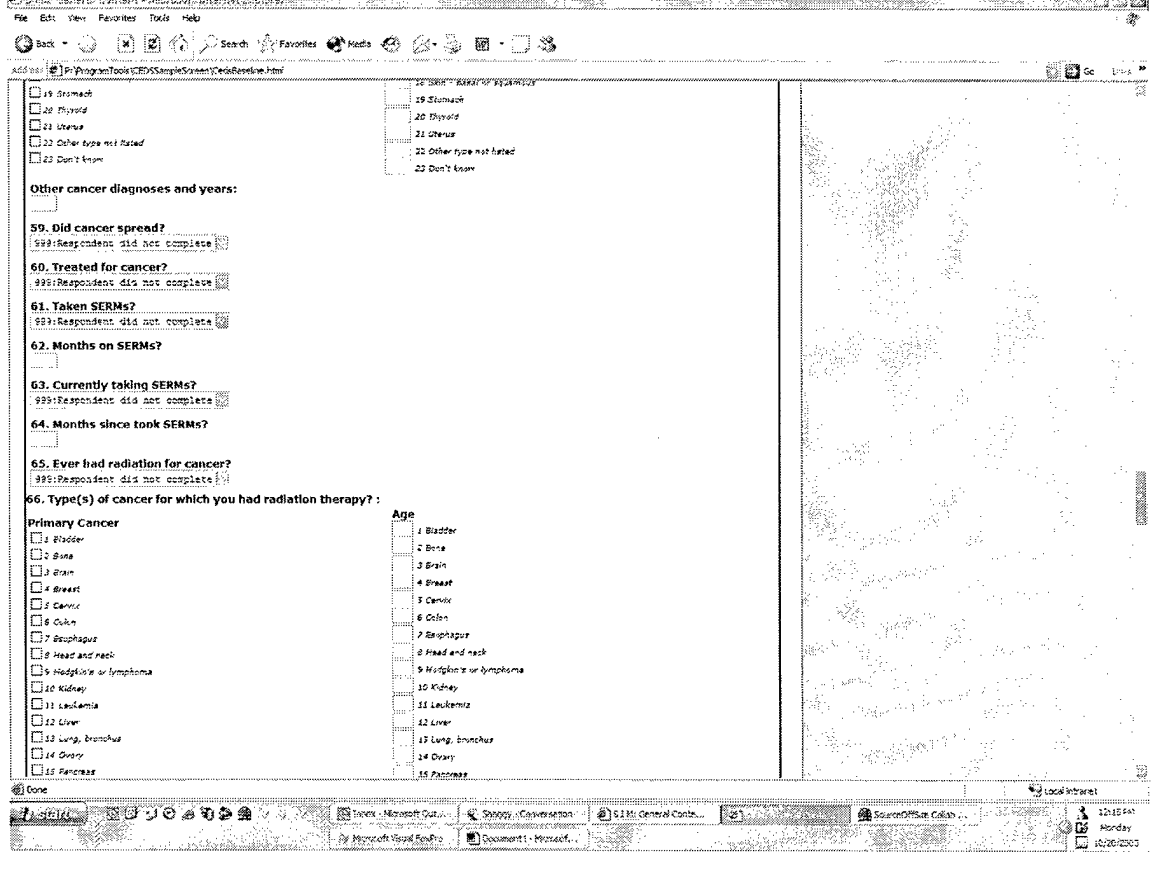
55a. Other mutated genes:

56. What was the result of your genetic test?
999:Respondent did not complete

57. Ever been diagnosed with cancer?
0:No

58. Type(s) of cancer with which you have been diagnosed? :

Primary Cancer	Diagnosis Year
1 Bladder	1 Bladder
2 Bone	2 Bone
3 Brain	3 Brain
4 Breast	4 Breast
5 Cervix	5 Cervix
6 Colon	6 Colon
7 Esophagus	7 Esophagus
8 Head and neck	8 Head and neck
9 Hodgkin's or lymphoma	9 Hodgkin's or lymphoma
10 Kidney	10 Kidney
11 Leukemia	11 Leukemia
12 Liver	12 Liver
13 Lung, bronchus	13 Lung, bronchus
14 Ovary	14 Ovary
15 Pancreas	15 Pancreas
16 Rectum	16 Rectum
17 Skin - Melanoma	17 Skin - Melanoma
18 Skin - basal or squamous	18 Skin - basal or squamous
19 Stomach	19 Stomach
20 Thyroid	20 Thyroid
21 Uterus	21 Uterus
22 Other type not listed	22 Other type not listed
23 Don't know	23 Don't know



Other cancer diagnoses and years:

59. Did cancer spread?
999:Respondent did not complete

60. Treated for cancer?
999:Respondent did not complete

61. Taken SERMs?
999:Respondent did not complete

62. Months on SERMs?

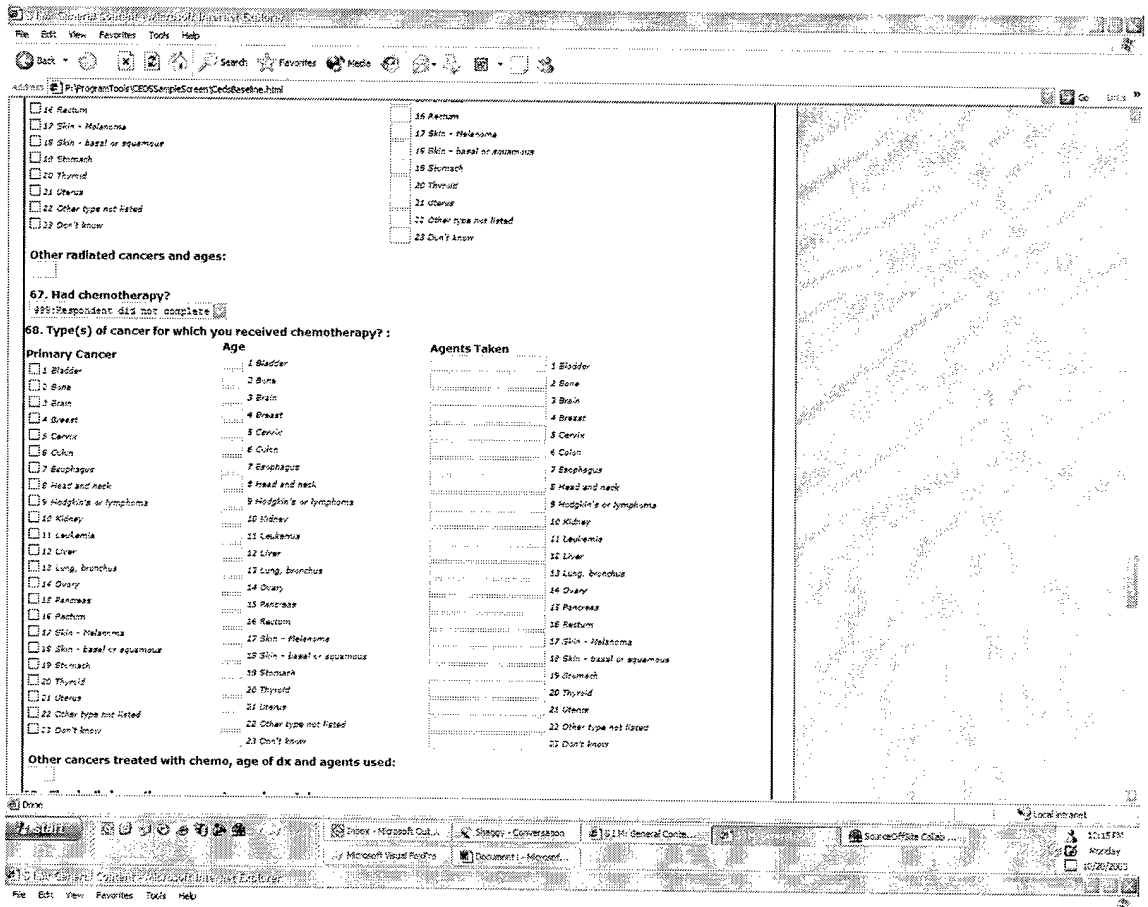
63. Currently taking SERMs?
999:Respondent did not complete

64. Months since took SERMs?

65. Ever had radiation for cancer?
999:Respondent did not complete

66. Type(s) of cancer for which you had radiation therapy? :

Primary Cancer	Age
1 Bladder	1 Bladder
2 Bone	2 Bone
3 Brain	3 Brain
4 Breast	4 Breast
5 Cervix	5 Cervix
6 Colon	6 Colon
7 Esophagus	7 Esophagus
8 Head and neck	8 Head and neck
9 Hodgkin's or lymphoma	9 Hodgkin's or lymphoma
10 Kidney	10 Kidney
11 Leukemia	11 Leukemia
12 Liver	12 Liver
13 Lung, bronchus	13 Lung, bronchus
14 Ovary	14 Ovary
15 Pancreas	15 Pancreas



16 Rectum
17 Skin - Melanoma
18 Skin - basal or squamous
19 Stomach
20 Thyroid
21 Uterus
22 Other type not listed
23 Don't know

Other radiated cancers and ages:

67. Had chemotherapy?

999:Respondent did not complete

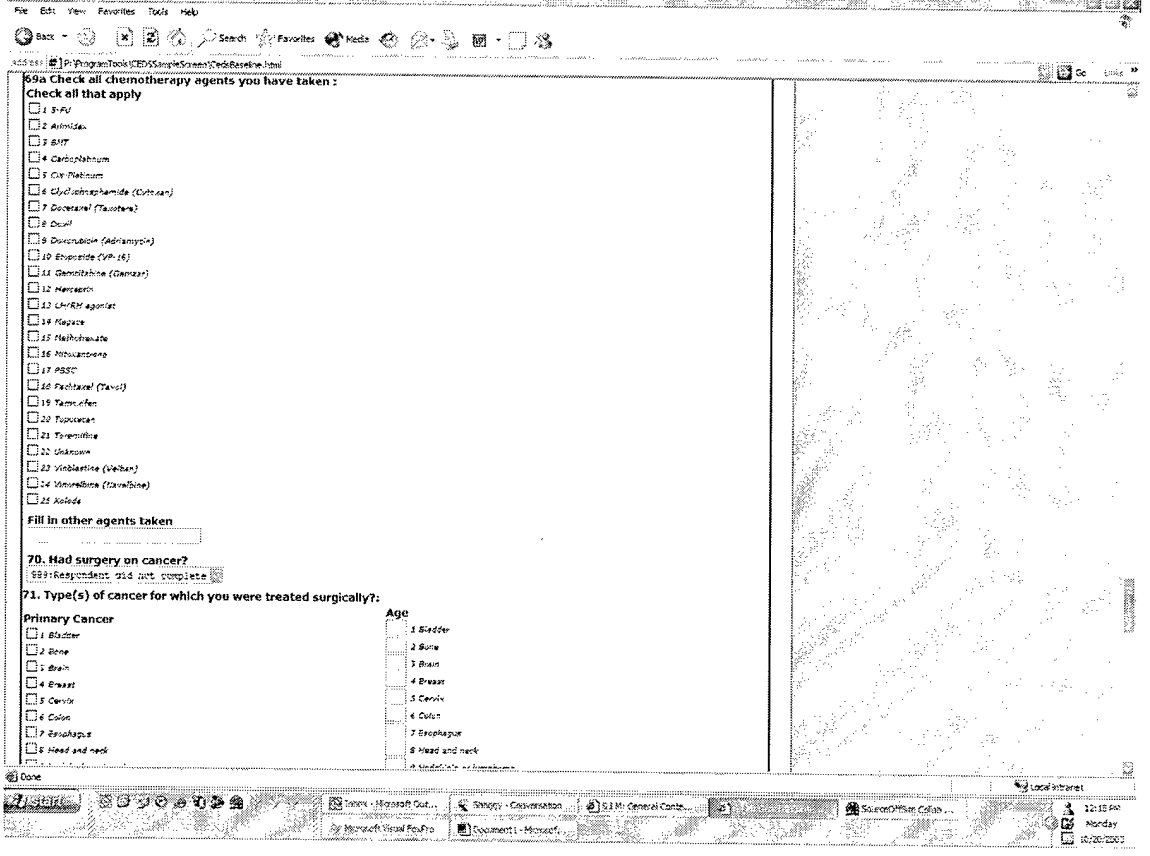
68. Type(s) of cancer for which you received chemotherapy? :

Primary Cancer	Age	Agents Taken
1 Bladder	1 Bladder	1 Bladder
2 Bone	2 Bone	2 Bone
3 Brain	3 Brain	3 Brain
4 Breast	4 Breast	4 Breast
5 Cervix	5 Cervix	5 Cervix
6 Colon	6 Colon	6 Colon
7 Esophagus	7 Esophagus	7 Esophagus
8 Head and neck	8 Head and neck	8 Head and neck
9 Hodgkin's or lymphoma	9 Hodgkin's or lymphoma	9 Hodgkin's or lymphoma
10 Kidney	10 Kidney	10 Kidney
11 Leukemia	11 Leukemia	11 Leukemia
12 Liver	12 Liver	12 Liver
13 Lung, bronchus	13 Lung, bronchus	13 Lung, bronchus
14 Ovary	14 Ovary	14 Ovary
15 Pancreas	15 Pancreas	15 Pancreas
16 Rectum	16 Rectum	16 Rectum
17 Skin - Melanoma	17 Skin - Melanoma	17 Skin - Melanoma
18 Skin - basal or squamous	18 Skin - basal or squamous	18 Skin - basal or squamous
19 Stomach	19 Stomach	19 Stomach
20 Thyroid	20 Thyroid	20 Thyroid
21 Uterus	21 Uterus	21 Uterus
22 Other type not listed	22 Other type not listed	22 Other type not listed
23 Don't know	23 Don't know	23 Don't know

Other cancers treated with chemo, age of dx and agents used:

Done

Local intranet



69a Check all chemotherapy agents you have taken :

Check all that apply

1 5-FU
2 Adriamide
3 BMT
4 Carboplatinum
5 Cis-Platinum
6 Cyclophosphamide (Cytoxan)
7 Docetaxel (Taxotere)
8 Doxil
9 Doxorubicin (Adriamycin)
10 Etoposide (VP-16)
11 Gemcitabine (Gemzar)
12 Herceptin
13 LHrRH agonist
14 Neupace
15 Nolitchemate
16 Nitroxantrone
17 PSSC
18 Paclitaxel (Taxol)
19 Tamoxifen
20 Topotecan
21 Toremifine
22 Unknown
23 Vinblastine (Velban)
24 Vinorelbine (Navelbine)
25 Xeloda

Fill in other agents taken

70. Had surgery on cancer?

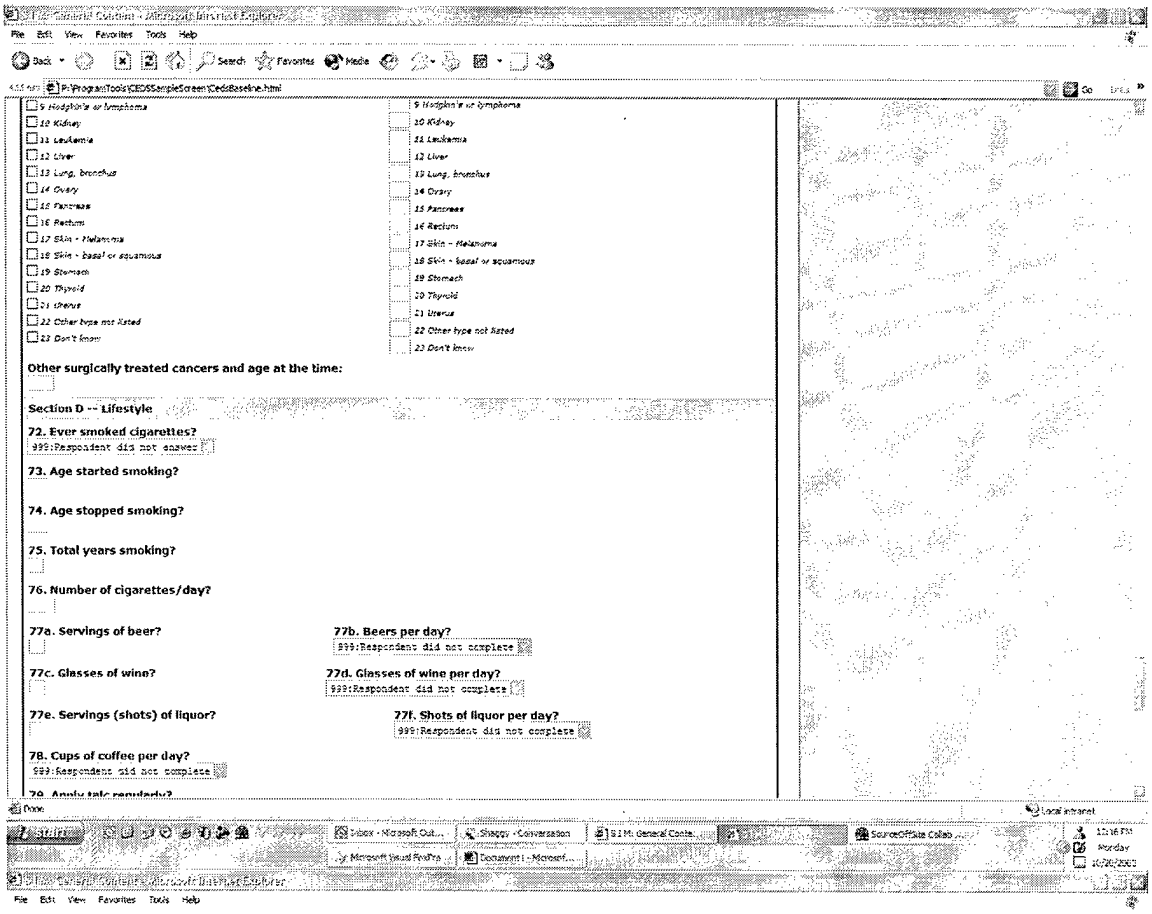
999:Respondent did not complete

71. Type(s) of cancer for which you were treated surgically?:

Primary Cancer	Age
1 Bladder	1 Bladder
2 Bone	2 Bone
3 Brain	3 Brain
4 Breast	4 Breast
5 Cervix	5 Cervix
6 Colon	6 Colon
7 Esophagus	7 Esophagus
8 Head and neck	8 Head and neck

Done

Local intranet



9 Hodgkin's or lymphoma
10 Kidney
11 Leukemia
12 Liver
13 Lung, bronchus
14 Ovary
15 Pancreas
16 Rectum
17 Skin - Melanoma
18 Skin - basal or squamous
19 Stomach
20 Thyroid
21 Uterus
22 Other type not listed
23 Don't know

Other surgically treated cancers and age at the time:

Section D -- Lifestyle

72. Ever smoked cigarettes?
999:Respondent did not answer

73. Age started smoking?

74. Age stopped smoking?

75. Total years smoking?

76. Number of cigarettes/day?

77a. Servings of beer?

77b. Beers per day?
999:Respondent did not complete

77c. Glasses of wine?

77d. Glasses of wine per day?
999:Respondent did not complete

77e. Servings (shots) of liquor?

77f. Shots of liquor per day?
999:Respondent did not complete

78. Cups of coffee per day?
999:Respondent did not complete

79. Apply talc regularly?
999:Respondent did not complete

80. Frequency of talc use?
999:Respondent did not complete

81. Years using talc?

82a. Check all talcs used? :
Types of talc used?

1 Baby powder - with talc
2 Baby powder - without talc
3 Body powder - with talc
4 Body powder - without talc
5 Body powder - with talc
6 Shower to Shower
7 Estee Lauder powder
8 Jean Nate bath powder
9 Johnson & Johnson baby powder
10 Avon baby powder
11 Avon's Imari powder
12 Elf's lavender silky body powder - talc
13 Scented powder from Jafra
14 Stork's Choice baby powder
15 White Shoulders bath powder
16 Wine Shoulders bath talc
17 Other powders - one or more with talc
18 Other powders - none containing talc
99 Unknown/Don't know

Other types of talc used?

83a. Number of chest x-rays?
999:Respondent did not complete

83b. Number of dental x-rays?
999:Respondent did not complete

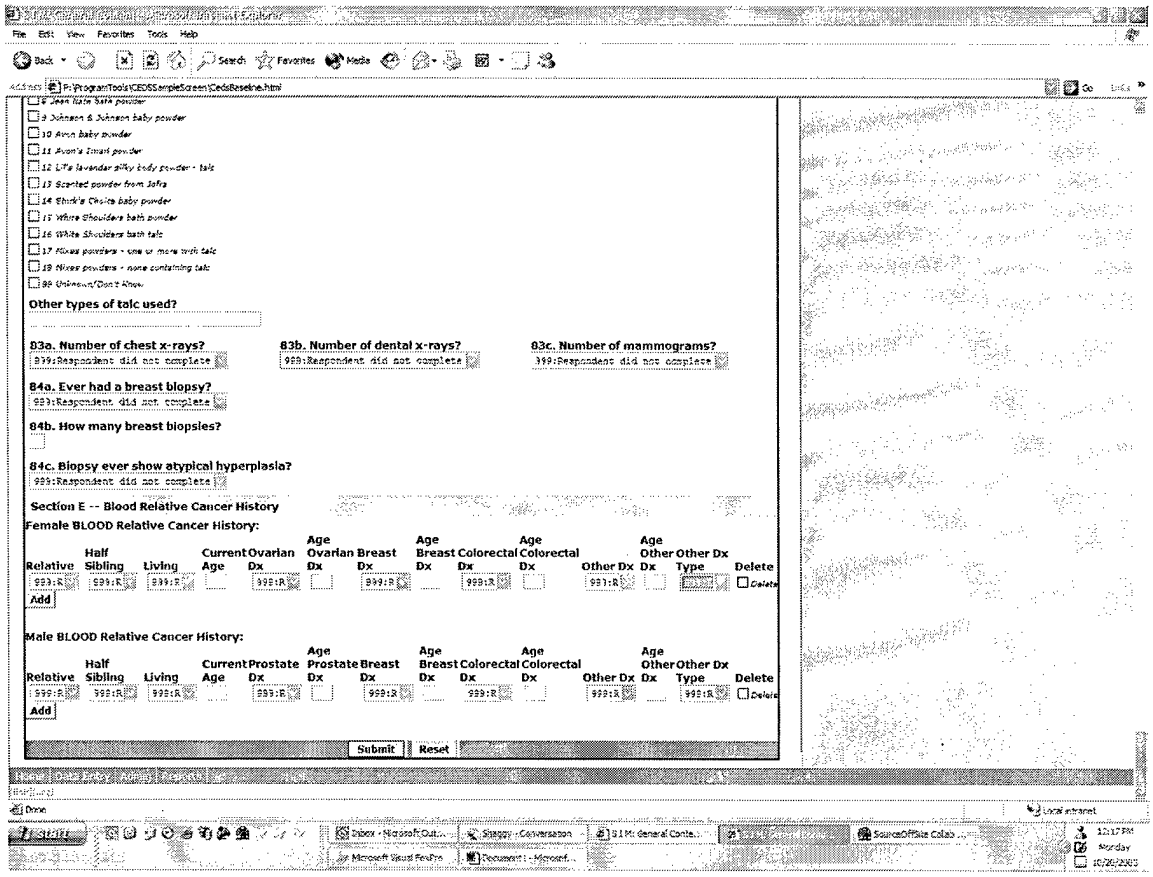
83c. Number of mammograms?
999:Respondent did not complete

84a. Ever had a breast biopsy?
999:Respondent did not complete

84b. How many breast biopsies?

84c. Biopsy ever show atypical hyperplasia?
999:Respondent did not complete

Section E -- Blood Relative Cancer History


File Edit View Favorites Tools Help
Back Search Favorites Media
Address P:\Program\Tools\CEDSSampleScreen\CedsBaseline.html
9 Jean Nate bath powder
9 Johnson & Johnson baby powder
10 Avon baby powder
11 Avon's Zimark powder
12 Lil's lavendar silky body powder - talc
13 Scented powder from Soho
14 Think's Choice baby powder
15 White Shoulders bath powder
16 White Shoulders bath talc
17 Mixes powders - one or more with talc
18 Mixes powders - none containing talc
88 Unknown/Don't Know
Other types of talc used?
83a. Number of chest x-rays?
999:Respondent did not complete
83b. Number of dental x-rays?
999:Respondent did not complete
83c. Number of mammograms?
999:Respondent did not complete
84a. Ever had a breast biopsy?
999:Respondent did not complete
84b. How many breast biopsies?
84c. Biopsy ever show atypical hyperplasia?
999:Respondent did not complete
Section E -- Blood Relative Cancer History
Female BLOOD Relative Cancer History:
Relative
Half Sibling
Living
Current Age
Ovarian Dx
Age Ovarian Dx
Breast Dx
Age Breast Dx
Colorectal Dx
Age Colorectal Dx
Other Dx
Age Other Dx
Other Dx Type
Delete
999:R
Add
Male BLOOD Relative Cancer History:
Relative
Half Sibling
Living
Current Age
Prostate Dx
Age Prostate Dx
Breast Dx
Age Breast Dx
Colorectal Dx
Age Colorectal Dx
Other Dx
Age Other Dx
Other Dx Type
Delete
999:R
Add
Submit
Reset
Done
Local intranet
Start
Inbox - Microsoft Out...
Staggs - Conversation
SourceOffsite Collab ...
Microsoft Visual FoxPro
Document1 - Microsof...
12:17 PM
Monday
10/20/2003

Appendix G
Conference Call Meeting Minutes

Cedars/COE Conference Call
September 10, 2003
1:30-2:30pm
Met Park 973

I. Updates

A. Breast Cancer Early Detection Study Protocol (*Judy/Scott*)

DoD format protocol: transfer COE/FHCRC human subject protocol to COE/Cedar-Sinai clinical protocol.

Issue: how are specimen tissue processed? Do we use our tissue specimen processing protocol or use the protocol at Cedar-Sinai? Send protocol to Carol for edits. Scott approved of adopting FHCRC protocol, but FHCRC TOR group has never processed breast tissue in the past: only for ovarian tissue. Scott will work with Kate on protocol.

B. Patient Pathology (*Scott*)

Create scan-able form for use in the COE and in Avon. Copy pages 3 and 4 of the form as many times depending on number of histological reports.

Need another questionnaire about biopsy and how tissue was obtained.

Pre-diagnosis make-up: need to know where data would come from. Filling out initial patient questionnaire and review medical information if not enough obtained from questionnaire.

Form requires pre-operative procedure. Do we want to know what's present at the day of or do we want recent history? Nicole brought up pathology reports generated at different times. Scott suggests only those in the past 3 months. Add bottom-line diagnosis. Add procedure and surgical site along with individual diagnosis.

Histology pages: more information about individual report. Scott will convert into digital format. Nicole would like to share questionnaire with other COE investigators especially Allen Gown and Eric Ross from Fox Chase who was in the process of creating such a questionnaire.

C. Yearly All-Investigator Meeting (*Leah)*

Shoot for January.

II. Subcontract Update (*Leah)*

Lisa has sent out subcontract agreements with a start date of September 21, 2003 and an activation date on November 1, 2003. It will take this long for both parties to sign off on agreements, but investigators may use the funds from the subcontract prior to the

activation date. Because we do not have human subject approval to date, there is a restriction in this first year award, but when the awards are extended into the second year, the restriction will be removed once human subject approval is received.

III. Other Business

Luminex: sold through BIORAD, allows multiplexing, high throughput, requires very small quantity of sample

Nicole would like biomarkers that distinguish comedo-DCIS. Leah will send abstracts.

Develop investigator meeting to include other COE investigators.

COE Conference Call: Cedars and FHCRC
July 30, 2003
1:00 to 2:00pm, PDT
Minutes

Please contact Kate Watabayashi at **kwatabay@fhcrc.org** or (206) 667-5624, with any questions or amendments to the minutes.

Call Participants:

Cedars-Sinai: Scott Karlan, Beth Karlan, Carole Baker

FHCRC: Nicole Urban, Judy Nelson, Shirley Gough, Kate Watabayashi, Samantha Hoyt, Joan McAree, Carole Shaw

Distribution List:

Scott Karlan, Beth Karlan, Carole Baker, Phyllis Lopez, Nicole Urban, Judy Nelson, Shirley Gough, Kate Watabayashi, Samantha Hoyt, Joan McAree, Carole Shaw, Ksenia Koon, Kathy O'Briant, Vandana Oza, Susie Wilson, Garnet Anderson, Martin McIntosh, Charles Drescher, Rae Lynn Baldwin, Kate Walla

Study Updates

Cedars: Cedars is still in the process of revising their forms and study materials to submit to their IRB committee. So far Cedars plans to enroll only women having Mammotome biopsies and estimate to enroll approximately 50-100 per year.

FHCRC: Have enrolled and collected blood from 6 biopsy patients. Plan to start enrolling women receiving screening mammograms in August.

Data Collection Instruments

Scott and Carole reviewed the patient pathology at dx form that was distributed at the previous conference call. Scott pointed out that in order to collect the appropriate data from these pathology reports and various participant records, we would need to change the format of our form. For example, on the original form we only allowed staff to check one type of disease diagnosis, whereas Scott pointed out that many women have multiple types of disease each with their own specific histology and pathology information that should be collected in order to get a complete picture of a woman's overall diagnosis and disease state.

Scott and his staff developed an outline of what they envision the form should look like and they will continue to develop and test this form over the next two weeks before drafting a final version that they will send to all investigators for review. This draft already includes pathology information on benign disease as well as cases.

Cedars plans to send out the Baseline Questionnaire in advance rather than giving it to women during their appointment. In principle it is fine for women to complete the questionnaire either pre or post-surgery, however during future calls we will discuss restricting this interval to a specific timeframe and what that timeframe should be.

Data Submission

Cedars currently use scannable teleforms to collect and transfer data. Carole will explore the feasibility of using these forms at FHCRC. In the meantime, Cedars has agreed to enter participant and specimen data into their own system, and then electronically transfer the data to the FHCRC database in batches. Both Kate Walla and Rae Lynn Baldwin are database contacts at Cedars. Carole will work with them as she develops the database.

Additional Items

1. Scott reported that so far at Cedars it has been very difficult to enroll women to donate tissue before their initial biopsy and diagnosis. Therefore most of the women they collect tissue from will be after the initial intervention (biopsy).

Action Items

1. Scott and his staff will continue to develop the patient pathology forms and when complete will send copies to the other investigators for review.

Appendix H
All-Investigator Meeting
Draft Agenda

All-Investigator Meeting: Draft Agenda
January 30, 2004
Fred Hutchinson Cancer Research Center, Seattle, WA.

Time	Speaker	
8:30am	Opening remarks - Nicole Urban, ScD	
9:00am	Nora Disis, MD - Cyclin D1, Cathepsin, Topoisomerase IIA	
9:20am	Gary Mann,MD - IGFBP-2, Her2/neu, p53	Biomarker Status and Evaluation
9:40am	Nancy Kiviat, MD - Mammoglobin	
10:00am	Gordon Mills, PhD - Lysophosolipids	
10:20am	Allen Gown, MD – VEGF, HGF, Immunohistochemistry Analysis	
10:40am	Break	
11:00am	Guest Speaker - Kornelia Polyak: "Molecular Markers *In Situ* Ductal Carcinoma of the Breast	
noon	Lunch	
1:00pm	Ingegerd Hellstrom, MD PhD - Antibody and Assay Development	Biotechnologies
1:20pm	Scott Karlan, MD/ Beth Karlan, MD - Gene Expression in Tissue	
1:40pm	Saul Rivkin, MD – Marsha Rivkin Center	Clinical and Patient Focus
2:00pm	Swedish Medical Center Surgeon-TBD	
2:20pm	Swedish Medical Center Surgeon-TBD	
2:40pm	Break	
3:00pm	Guest Speaker - BioRad Luminex: Bead-based Fluorescent Multiplex Protein Analysis Systems	
4:00pm	Discussion	
5:00pm	Closing	